OPENING NEW AVENUES FOR NICKEL-CATALYZED CYCLOADDITIONS

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

New catalytic approaches to carbocycles and heterocycles are disclosed. The long-standing challenge of using ketenes in transition-metal catalyzed cycloaddition is successfully addressed by using Ni–phosphine complexes. These complexes catalyzed the cycloaddition of various ketenes and diynes. In general, 2,4-cyclohexadienones were formed instead of products arising from decarbonylation of the ketenes. Efforts to develop the asymmetric version of this cycloaddition chemistry are also discussed.

The inability of Ni-phosphine complexes to promote the oxidative coupling of alkyne and nitrile was successfully addressed using the catalytic combination of $Ni(cod)_2$ and Xantphos. This catalyst system was used to couple a variety of diynes and unactivated nitriles to form pyridines. The reaction proceeds under ambient conditions to provide excellent yields of the products. Comparison of this catalyst with the other state-of-the-art catalysts is also provided.

An easy and expeditious route to substituted piperidines is also described. A Ni-phosphine complex was used as catalyst for [4 + 2] cycloaddition of 3-azetidinone and alkynes. This unique reaction has broad substrate scope and affords piperidines in excellent yields and excellent regioselectivity. In the reaction of an enantiopure azetidinone, complete retention of stereochemistry was observed.

3-Azetidinone and a variety of diynes also undergo a cycloaddition reaction catalyzed by Ni/IPr to give [5-8] fused dihydroazocine compounds. The reaction involves a

challenging $C(sp^2)$-$C(sp^3)$ bond cleavage step, yet, surprisingly, proceeds at low temperature. Interestingly, in the case of 2,7-diynes, a spirocyclic pyran product was obtained instead of a [6-8] fused dihydroazocine. This strategy was also extended to oxetanone to access oxocines.

A novel mode of reactivity of tropone is disclosed. A variety of diynes were efficiently coupled with tropone using a nickel catalyst to afford tricyclic products. Unsymmetrical diynes were successfully coupled to yield cycloadducts with high regioselectivity. Additionally, biaryls and triaryl frameworks can be easily accessed in a single, chemical operation in good yields and with excellent regiocontrol.

To my family

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LIST OF ABBREVIATIONS

BINAM-P - $N^2,N^{2'}$-bis(diphenylphosphino)-[1,1'-binaphthalene]-2,2'-diamine

BINAP – 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene

Bnh – benzhydryl

Boc – *tert*-butoxycarbonyl

Cl-OMe-BIPHEP - (5,5'-dichloro-6,6'-dimethoxy-[1,1'-biphenyl]-2,2'-diyl)bis(diphenyl-phosphine)

COD – cyclooctadiene

Cp – cyclopentadienyl

Cy – cyclohexyl

Cyp – cyclopentyl

$CyPPh_2$ – cyclohexyldiphenylphosphine

DCE – 1,2-dichloroethane

DCM – dichloromethane

DCPE – 1,2-bis(dicyclohexylphosphino)ethane

DMAP – 4-dimethylaminopyridine

DMF - dimethylformamide

DPPB – 1,2-bis(diphenylphosphine)butane

DPPE – 1,2-bis(diphenylphosphino)ethane

DPPF – 1,1'-bis(diphenylphosphine)ferrocene

ESI – electron spray ionization

Et – ethyl

GC – gas chromatography

H8-BINAP – 2,2'-bis(diphenylphosphino)-5,5',6,6',7,7',8,8'-octahydro-1,1'-binaphthyl

RT – room temperature

i-Pr – isopropyl

I*i*Pr – 1,3-diisopropyl-imidazol-2-ylidene

IMes – 1,3-bis-(2,4,6-trimethylphenyl)-imidazol-2-ylidene

IPr – 1,3-bis-(2,6-diisopropylphenyl)-imidazol-2-ylidene

m-CPBA – *meta*-chloroperbenzoic acid

$MePPh_2$ – methyldiphenylphosphine

Ni(COD)2 – Bis(1,5-cyclooctadiene)nickel

NMDPP – neomenthyldiphenylphosphine

nOe – nuclear Overhauser effect

NOESY-1D – one dimensional nuclear Overhauser spectroscopy

OMe-BIPHEP - (6,6'-dimethoxy-[1,1'-biphenyl]-2,2'-diyl)bis(diphenylphosphine)

PCy_3 – tricyclohexylphosphine

PG – protecting group

PEt_3 – triethylphosphine

Ph – phenyl

P*n*Bu_3 – tri(n-butyl)phosphine

P(*o*-Tol)$_3$ – tri(o-tolyl)phosphine

PPh_3 – triphenylphosphine

SEGPHOS – 4,4'-bi-1,3-benzodioxole-5,5'-diylbis(diphenylphosphine)

SIBen – 1,3-dibenzyl-imidazol-2-ylidene

SIPr – 1,3-bis(2,6-diisopropylphenyl)-imidazolin-2-ylidene

Skewphos - (2*S*,4*S*)-pentane-2,4-diylbis(diphenylphosphine)

Synphos – 6,6'-bis(diphenylphosphino)2,2',3,3'-tetrahydro-5,5'-bi-1,4-benzodioxin

t-Bu – tert-butyl

THF – tetrahydrofuran

TMS – trimethylsilyl

Tol- tolyl

Ts – tosyl

CHAPTER 1

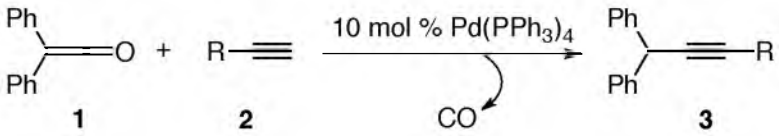
NICKEL-CATALYZED KETENE CYCLOADDITION: A SYSTEM THAT RESISTS THE FORMATION OF DECARBONYLATION SIDE PRODUCTS

Introduction

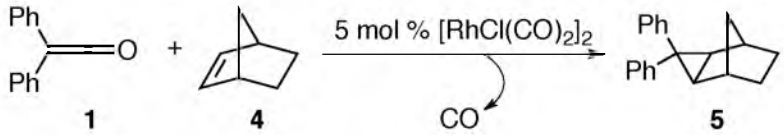
Transition-metal-catalyzed cycloaddition reactions have proven to be an excellent strategy to access important cyclic compounds. Generally, these processes utilize unsaturated starting materials like alkynes, alkenes, and dienes to provide carbocyclic products.[1] Over the past few decades, this approach has been significantly advanced to incorporate carbon dioxide, isocyanates, nitriles, and carbonyls as an unsaturated coupling partner to afford various types of heterocycles.[2] A variety of metal catalysts (Co, Rh, Ir, Ni, Pd) have been developed to effect these transformations. Despite the rich history of cycloaddition chemistry, ketene substrates are notoriously absent.[3]

In this regard, the reaction of ketenes with transition metal complexes is not the problem.[4] In fact, ketenes easily form η^2 complexes with various transition metals.[5] The origin of this ketene reactivity can be easily explained on the basis of frontier molecular orbital theory.[4] The localization of the lowest unoccupied molecular orbital (LUMO) on the beta carbon, and the highest occupied molecular orbital (HOMO) on the alpha-carbon as well as the oxygen atom, essentially gives rise to two modes of coordination of

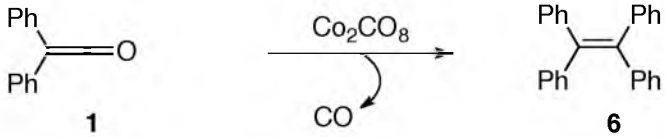
can be attributed to their propensity to decarbonylate and form stable, unreactive metal-carbonyl complexes.[4-6] In an attempt to couple ketenes with alkynes, Watanabe and coworkers discovered that catalytic amount of $Pd(PPh_3)_4$ caused the decarbonylation of ketene **1**, and coupled the resulting transient species with alkyne **2** as shown in eq 1.1. Similarly, decarbonylation of ketene has also been witnessed when ketene **1** and norbornene **4** were subjected to a Rh-catalyst (eq 1.2). Notably, stoichiometric Co_2CO_8 has also been found to cause the decarbonylation of diphenyl ketene to afford the tetra-phenyl substituted alkene **6** (eq 1.3). Hoberg and Miyashita independently studied the interaction of ketene with Ni-phosphine (Ni-PPh_3) complexes (Scheme 1.1). The Ni-PPh_3 easily reacts with phenyl-methyl ketene **7** at -40 °C to afford an η^2 C-O bound Ni-ketene complex **8**, which on warming up to room temperature leads to decarbonylation products.



1 **2** **3** (eq 1.1)

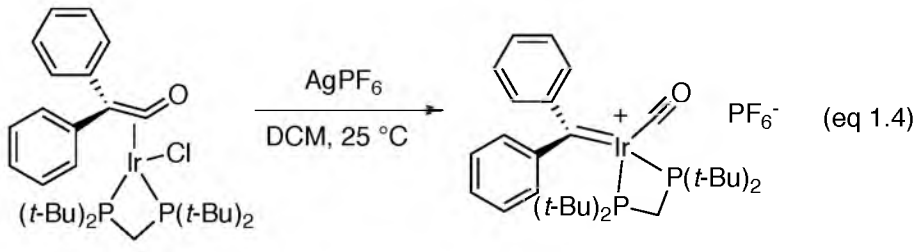


1 **4** **5** (eq 1.2)



1 **6** (eq 1.3)

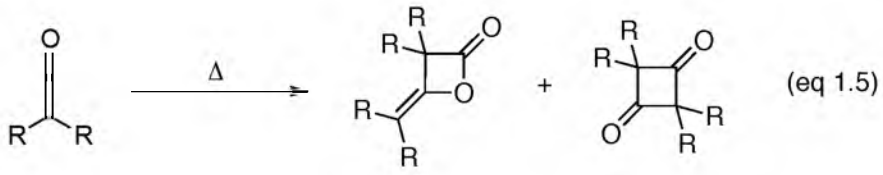
Remarkably, Grotjahn and coworkers discovered a C-C-bound Iridium-ketene complex **12**, which on reaction with silver salt such as $AgPF_6$ leads to decarbonylation product **13** as shown in eq 1.4. In stark contrast to these findings, the monodentate phosphine-ligated iridium complex forms a C-O-bound iridium-ketene complex **14** (Scheme 1.2). To explore the reactivity of these complexes with alkynes, the authors prepared several alkyne and ketene coordination complexes (e.g. **17**) of iridium by two alternate routes: (a) reaction of iridium-ketene complex with an alkyne, or (b) reaction of an iridium-alkyne complex with ketene. Besides the C-C-bound ketene and alkyne, iridium also binds with the pendant arene of a ketene in a η^2 fashion. To promote the oxidative coupling of alkyne and ketene, the coordination complex was heated to 60 °C. Notably, no oxidative coupling products **21** or **22** were observed, instead, the reaction takes a different course. That is on heating, this unique alkyne-ketene iridium complex **17** transforms into an iridabenzopyran metallacycle **20**, as shown in Scheme 1.2. The authors proposed that the iridium alkyne-ketene complex undergoes C-H activation (**18**), followed by alkyne insertion to afford a vinyl-iridium complex **19**. Finally, the insertion of ketene across iridium-vinyl bond leads to the observed metallacycle **20**. Assuming the fact that this reactivity may be unique in the case of diphenyl ketene **1**, Grotjahn and coworkers performed the similar study using phenyl-methyl ketene.



12 **13** (eq 1.4)

Interestingly, an iridium-hydride complex was formed when an iridium-alkyne complex was exposed to phenyl-methyl ketene at 60 °C (Scheme 1.3). To promote the reductive elimination of this stable complex, CO was introduced in the system, which eventually led to the formation of an iridium carbonyl complex as well as a dienone. To account for the surprising formation of the iridium hydride species, the authors propose a four-step mechanism, which involves the initial sp^3 C-H activation of ketene that leads to a η^3-iridium complex. The subsequent alkyne insertion followed by reductive elimination affords a dienone coordinated iridium complex. Finally, the sp^2 C-H activation of the coordinated dienone affords the observed iridacycle.

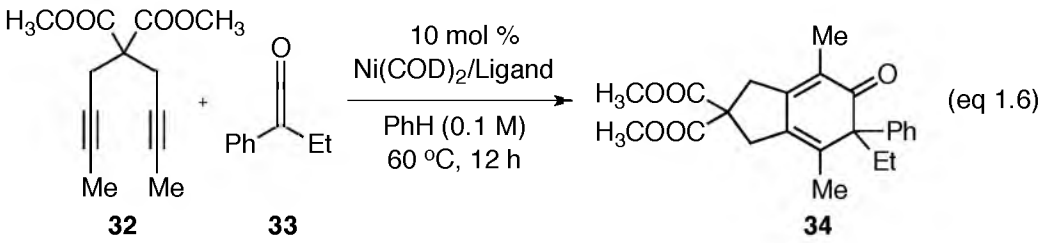
Another issue concerning ketenes is that these often undergo homo-dimerization under thermal conditions to afford cyclobutane-diones or alkylidenyl-lactones (eq 1.5).[7] In summary, the high tendency of metal-ketene complexes to undergo decarbonylation, the inability of metal-ketene complexes to undergo a fruitful oxidative coupling event with alkyne, and poor thermal stability of various ketenes thwarted previous attempts to use ketenes in its full integrity in transition-metal catalysis. In view of these pitfalls, we were surprised and delighted to discover that Ni-phosphine catalysts mediate the cycloaddition of ketenes and diynes to afford 2,4-cyclohexadienones in good yields.[8-9] Herein, we report these results.



(eq 1.5)

Results and discussions

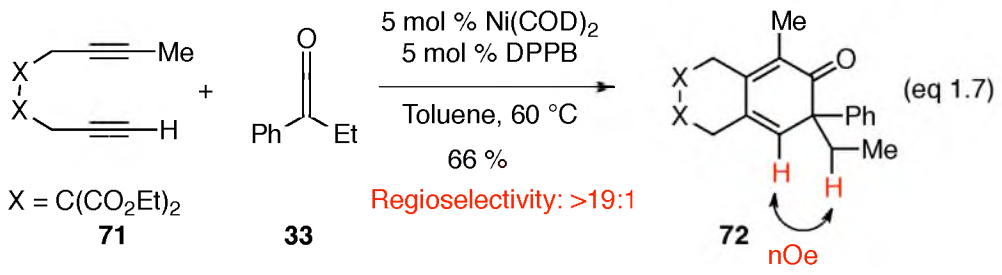
To effect the cycloaddition of diynes **32** and ketenes **33**, Dr. Dawn M. Troast evaluated a variety of ligands in conjunction with $Ni(COD)_2$ as a Ni (0) precursor. Diyne **1** and phenyl-ethyl ketene **a** were chosen as model substrates for this study (eq 1.6). Notably, the highly σ-donating *N*-heterocyclic carbenes (NHCs), which were found to be extremely active ligands in other reported Ni-catalyzed cycloaddition reactions, unfortunately exhibited poor performance (entries 1-5, Table 1.1). Next we turned our attention towards monodentate and bidentate phosphine ligands. In most cases, by-products arising from dimerization of the diyne and ketene were observed (entries 1–9, Table 1.2). However, we found that high yields were obtained when either DPPF or DPPB was employed as the ligand (entries 10 and 11, Table 1.2). When DPPF was employed as the ligand in the cycloaddition of other diyne substrates with phenyl-ethyl ketene, a complex mixture of diyne dimer, ketene dimer, and cycloadduct **34** was formed, hampering purification. In general, reactions run with DPPB were cleaner. Therefore, our optimized conditions employed DPPB as the ligand of choice. The cycloaddition afforded a carbocyclic product **34** that resulted from the coupling of the C=C bond of ketene **33** rather than a pyran, which would have resulted from the coupling of the C=O bond. I optimized this reaction further, which ultimately led to the following reaction conditions: 5 mol % catalyst loading ($Ni(COD)_2$ and DPPB in 1:1 molar ratio) at a 0.1 M reaction concentration in toluene at 60 °C.



The scope of this reaction was briefly investigated by Dr. Dawn M. Troast. After her departure, I collaborated with Dr. Rodrgio Cella to extensively investigate the substrate scope. Importantly, we found that ketenes other than **33** could be used as substrates in the cycloaddition reaction and that a variety of cyclohexadienones could be prepared with these optimized reaction conditions. For example, diyne **32** not only reacted with ketene **33** but also with a diaryl ketene **35** as well as a ketene with increased steric hinderance **37** (entries 1–3, Table 1.3). Diynes that are prone to cyclotrimerization side reactions, such as the phenyl substituted diyne **39** and terminal diynes **41** and **43**, were also successfully converted to their respective cyclohexadienone products **42** and **44** in moderate yields (entries 4–6).[10] The success of this cycloaddition may be attributed to the strong binding of ketenes with nickel, which outcompetes the cyclotrimerization reactions. In addition, cycloaddition products could be prepared from sulfonamide diynes **45** and ether-backbone diyne **49** (entries 7–9).

Diynes separated by a four-atom linker instead of a three-atom linker afforded cyclohexadienones in higher yields (entries 1-10, Table 1.4). For example, the reaction between diyne **51** and ketene **33** afforded the product **52** in 91% (vs. 82% with diyne **32**, entry 1, Table 1.4 vs. entry 1, Table 1.3). We found that aryl ketenes bearing an electron-withdrawing group in the *para*-position (-F, entry 4) enhanced the formation of the carbocyclic product whereas aryl ketenes bearing an electron-donating group in the *para*-

position (-OMe, -Me, entries 2-3) had the opposite effect. We believe that the presence of electron-withdrawing group on the phenyl ring makes the ketene more electron-deficient and more pi-acidic in nature, which increases its binding with nickel complex, and hence makes them more reactive than eletron-rich ketenes. Interestingly, the cycloaddition between diyne **51** and trimethylsilyl ketene **62** gave phenolic products **63** and **64** in 63:19 ratio. The formation of phenolic products could be due to a facile 1,3-silyl migration in the proposed cyclohexadienone intermediate, as shown in Figure 1.2.[11] The reaction of ketene **65** afforded a spiro-bicyclic product **66** in good yield (entry 8). Again, terminal diynes **67** and **69** were also found to afford carbocyclic products, as evidenced by the formation of **68** and **70** (entries 9 and 10, respectively). The standard reaction conditions were applied to unsymmetrical diyne **71**. We were delighted to selectively obtain one regioisomer **72** in 66% yield (eq 1.7). The regiochemistry of **72** was determined by NOESY-1D spectroscopy.



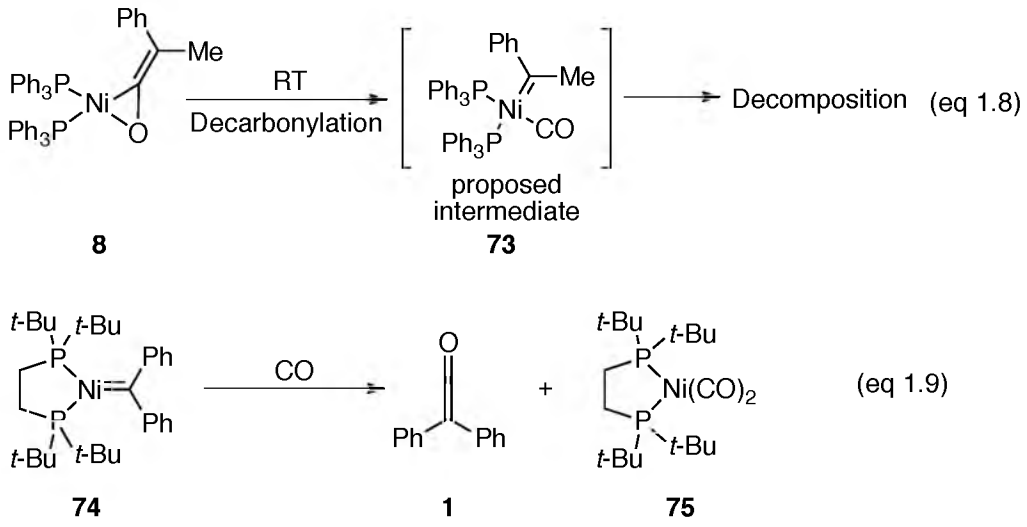
X = $C(CO_2Et)_2$

71 **33** **72**

Mechanism

The previous report by Miyashita clearly shows that Ni-ketene complexes start to decompose at a temperature above -40 °C. The decomposition products can be rationalized by the formation of Ni-carbene intermediate **73**, which may result from the decarbonylation of ketene (eq 1.8). Given these failures, the success of our nickel-

catalyzed cycloaddition of ketene is highly intriguing. In an isolated study on the reactivity of nickel-carbene species, Hillhouse has demonstrated that Ni-carbene complex **74** ligated with a bidentate ligand reacts with CO to afford a Ni-carbonyl compound **75** and diphenyl ketene **1** (eq 1.9). This piece of data suggests that the decarbonylation of ketene to carbene may be reversible. Our preliminary ^{31}P-NMR studies on DPPF-ligated C-O-bound phenyl-propyl ketene nickel-complex (for preparation, see Scheme 1.4) indicate their high thermal stability at room temperature as well as temperature as high as 60 °C. Further studies to gain more insight into the effect of ligands on the stability of nickel-ketene complexes is ongoing in our lab.



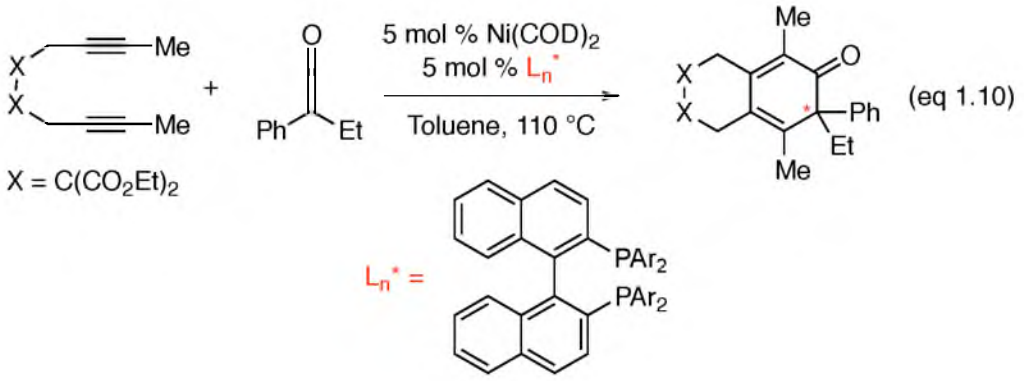
On the basis of the stability of nickel-ketene complex in presence of a bidentate ligand such as DPPF, two conventional mechanisms may be proposed to account for the formation of the cycloaddition product (Scheme 1.5). In proposed mechanism I, diyne can first undergo homocoupling (intermediate **A**) followed by insertion of ketene to give the intermediate **C** *nickelacycloheptadienone*, which would then undergo reductive elimination to give 2,4-cyclohexadienone. Alternatively, one of the arms (alkyne) of the

diyne can undergo oxidative coupling (intermediate **B**) with ketene followed by insertion of the tethered alkyne to again give intermediate **C** *nickelacycloheptadienone,* which would then undergo reductive elimination to 2,4-cyclohexadienone as shown in proposed mechanism II. The regioselectivity in this cycloaddition reaction is similar to other nickel-catalyzed cycloadditions reported by our lab, which suggests that the heterocoupling pathway may be operating. In the future, we intend to pursue a mechanistic study on this to gain critical insight into the mechanism. Specifically, the role of recently isolated stable nickel-ketene complexes in the catalytic cycle will also be investigated.

The enantioselective formation of quaternary stereocenters remains a formidable challenge to organic chemists. With this in mind, I collaborated with Dr. Rodrigo Cella to investigate the development of an asymmetric version of this cycloaddition reaction. In the beginning, we focused our attention on chiral bisphosphine ligands similar to DPPB (Table 1.5). We found that commercially available (S, S)-SKEWPHOS afforded the desired product in good yield but with an enantiomeric excess of only 40%. Unfortunately, other chiral DPPB analogs exhibited poor performance. The DPPB analogs containing stereogenic centers also did not fare any better. The poor enantiocontrol in case of conformationally flexible diphosphines suggested that a more rigid ligand might show improvement in enantioselectivity. Keeping this in mind, we next turned our attention towards structurally more rigid atropisomeric ligands.

Initial investigations employing (R)-BINAP as a ligand gave dismal results (Table 1.6). That is, no reaction was observed when standard reaction conditions (5 mol % catalyst, 0.1 M diyne, 60 °C, and toluene) were employed. However, carbocyclic product

was generated when the temperature was elevated to 80 °C. Although a relatively low yield (38%) was obtained, excellent enantioselectivity (99%) was observed. A higher yield was obtained when the reaction temperature was increased to 100 °C with only a slight decrease in *ee*. Further attempts to improve the yield of this reaction proved futile. So, to access the cycloadduct in high yields and excellent enantioselectivity, we then decided to test various types of atropisomeric bis-phosphine ligands which were either commercially available or could be easily synthesized using reported procedures. Out of all of these, *tol*-BINAP, *H8*-BINAP, SYNPHOS, and *H8*-BINAM-P exhibited product formation, but the yields were no better than when using BINAP. The SEGPHOS and its F_2-analog failed to provide any promising lead. However, the use of OMe-BIPHEP and Cl-OMe-BIPHEP led to moderate yield and only good enantiocontrol. After evaluation of various commercially available atropisomeric binaphthyl- and biphenyl-phosphines, we turned our focus back to BINAP ligand for excellent enantiocontrol. Since the yield was only moderate for our model substrate, we then decided to investigate the effect of electronics of ligands on the reaction yields (eq 1.10, Table 1.7). This systematic variation of electronics led us to an interesting discovery; the use of an electron-withdrawing group such as the trifluoromethyl group on the ligand surprisingly afforded the desired cycloadduct in very high yields. To further improve the yield of the reaction, we evaluated a bis-CF_3-biphenyl phosphine. The cycloadduct was formed in yield notably higher than even our racemic version with DPPB. With this result in hand, we prepared and evaluated the chiral bis-CF_3-biphenyl phosphine. Unfortunately, the enantiocontrol was poor and the desired product was formed in only 60 % *ee*. We believe that it could be due to the poor coordinating ability of electron-poor phosphine ligand.



Conclusion

In summary, we have successfully incorporated ketenes in [2+2+2] cycloaddition reactions with diynes. Decarbonylation of the ketene starting materials was not observed. Instead, a variety of 2,4-cyclohexadienones were formed. Enantionpure cyclohexadienone product was obtained when (R)-BINAP was used as the ligand. The use of other DPPB-based, binaphthyl-, and biphenyl chiral phosphine ligands, however, led to no significant improvement. Efforts to develop a general asymmetric catalyst system and to understand the mechanistic details of this cycloaddition chemistry are underway.

General experimental

All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2 filled glove box unless otherwise noted. Toluene was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. THF was freshly distilled from Na/benzophenone. $Ni(COD)_2$ was purchased from Strem and used without further purification. The ketenes **33**,[13a] **35**,[13b] **37**,[13c] **47**,[13d] **53**,[13c] **55**,[13d] **57**,[13e]

59,[13a] **62**,[13f] **65**,[13g] and diynes **32**,[14a] **39**,[14b] **41**,[14c] **43**,[14d] **45**,[14e] **49**,[14a] and **51**[14c] were prepared according to literature procedures. All other reagents were purchased and used without further purification unless otherwise noted.

^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 300 and 125 MHz, respectively, unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^{1}H and to the center line of a triplet at 77.23 ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, t, q, and quint stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, quartet, and quintet, in that order. All ^{13}C NMR spectra were proton decoupled. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer.

Gas Chromatography was performed on an Agilent 6890 gas chomatograph with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 °C; temperature ramp rate 50 °C/min.; final temperature: 300 °C held for 7 minutes; detector temperature: 250 °C.

Ligand screening

In a nitrogen-filled glove box, a stock solution of diyne (**32**, 1 equiv, 0.05 M) in benzene was prepared along with decane as standard in a clean and predried scintillation vial. The stock solution of ketene (**33**, 1.2 equiv) in benzene was also prepared in a separate vial. In separate vials, stock solutions of catalysts were prepared by mixing $Ni(COD)_2$ and ligands (see Table 1.2 for the molar ratio). 5 mol % Catalyst was added to the vial containing diyne and ketene. The vials were taken out of the glove box and

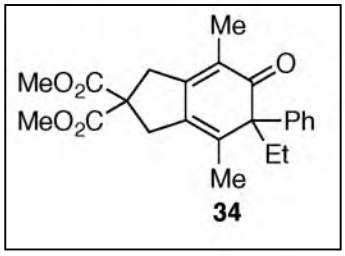
stirred at 60 °C for 12 h; after which, all the reaction vials were opened to air and then analyzed by GC.

General procedure for cycloaddition

In a nitrogen-filled glove box, a 5 mol % catalyst solution (prepared from $Ni(COD)_2$ and DPPB in 1:1 molar ratio in toluene) was added to the vial containing diyne (1 equiv., 0.1 M) and ketene (1.2 equiv.) in toluene. The vial was taken out of the glove box and stirred at 60 °C for 5 h, opened to air, concentrated *in vacuo,* and purified by silica gel flash column chromatography.

Dimethyl 5-ethyl-4,7-dimethyl-6-oxo-5-phenyl-5,6-dihydro-1H-indene-2,2(3H) dicarboxylate (**34**)

The general procedure was used with 41.8 mg (0.18 mmol, 0.1 M) of diyne **32**, 31.0 mg (0.21 mmol) of ketene **33**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford the title compound **34** as bright yellow sticky oil, 82% yield.

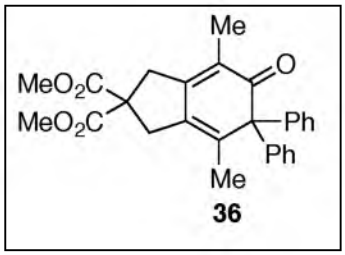


34

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.26-7.10 (m, 5H), 3.79 (s, 3H), 3.77 (s, 3H), 3.32 (s, 2H), 3.24 (d, J = 7.2 Hz, 2H), 2.63 (dq, J = 7.5 Hz, 14.9 Hz, 1H), 1.95 (dq, J = 7.5 Hz, 14.9 Hz, 1H), 1.79 (s, 3H), 1.61 (s, 3H), 0.64 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 203.3, 171.6, 154.6, 142.2, 141.6, 132.1, 128.8, 127.1, 126.9, 124.7, 61.4, 58.3, 53.3, 53.2, 39.7, 38.0, 29.9, 16.4, 11.6, 8.8. IR (CH_2Cl_2, cm^{-1}): 2956, 1736,

1648, 1437, 1263, 1204, 1076. HRMS (ESI) calcd for $C_{23}H_{26}O_5Na$ $[M+Na]^+$ 405.1678, found 405.1682.

Dimethyl 4,7-dimethyl-6-oxo-5,5-diphenyl-5,6-dihydro-1H-indene-2,2(3H)-dicarboxylate (**36**)

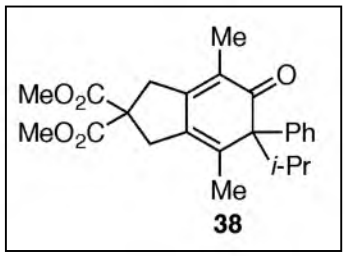


36

The general procedure was used with 50 mg (0.21 mmol, 0.1 M) of diyne **32**, 49.3 mg (0.25 mmol) of ketene **35**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 20% ethyl acetate in hexanes to afford the title compound **36** as yellow sticky oil, 50% yield.

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.26 (m, 6H), 7.15 (m, 4H), 3.75 (s, 6H), 3.32 (s, 2H), 3.25 (s, 2H), 1.80 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 203.3, 171.7, 153.5, 141.8, 141.5, 131.4, 129.9, 128.3, 127.3, 124.3, 68.3, 58.2, 53.4, 39.6, 38.1, 18.9, 12.0. IR (CH_2Cl_2, cm^{-1}): 2954, 2922, 1736, 1652, 1616, 1438, 1258, 1203, 1072. HRMS (ESI) calcd for $C_{27}H_{26}O_5Na$ $[M+Na]^+$ 453.1678, found 453.1693.

Dimethyl 5-isopropyl-4,7-dimethyl-6-oxo-5-phenyl-5,6-dihydro-1H-indene-2,2(3H)-dicarboxylate (**38**)



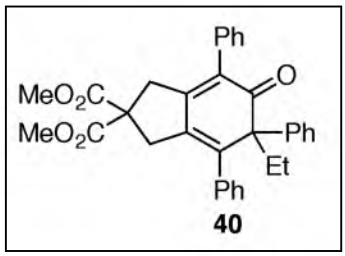
38

The general procedure was used with 119.0 mg (0.50 mmol, 0.1 M) of diyne **32**, 160 mg (1.0 mmol) of ketene **37**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford the title compound **38** as bright yellow liquid, 50% yield.

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.20 (m, 3H), 7.09 (d, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 3.29 (d, *J* = 6.3 Hz, 2H), 3.20 (s, 2H), 2.92 (septet, *J* = 6.9 Hz, 1H), 1.79 (s, 3H), 1.67 (s, 3H), 0.95 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 203.7, 171.7, 171.68, 153.7, 141.7, 141.4, 132.4, 128.8, 128.4, 126.7, 125.2, 65.7, 58.3, 53.3, 53.27, 39.6, 38.2, 35.4, 18.8, 17.5, 11.6. IR (CH_2Cl_2, cm^{-1}): 2959, 1737, 1438, 1265, 1074. HRMS (ESI) calcd for $C_{24}H_{28}O_5K$ $[M+K]^+$ 435.1574, found 435.1586.

Dimethyl 5-ethyl-6-oxo-4,5,7-triphenyl-5,6-dihydro-1H-indene-2,2(3H)-dicarboxylate (**40**)

The general procedure was used with 65.4 mg (0.18 mmol, 0.1 M) of diyne **39**, 31.8 mg (0.22 mmol) of ketene **33**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford the title compound **40** as bright yellow sticky oil, 65% yield.

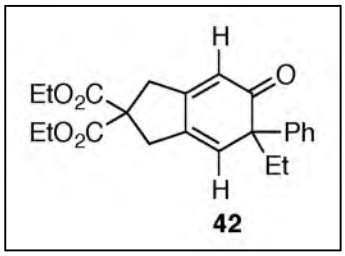


40

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.30 (m, 8H), 7.20 (m, 5H), 6.75 (d, *J* = 8.1 Hz, 2H), 3.77 (s, 3H), 3.72 (s, 3H), 3.23 (m, 4H), 2.72 (dq, *J* = 7.5 Hz, 14.7 Hz, 1H), 1.75 (dq, *J* = 7.2 Hz, 14.4 Hz, 1H), 0.84 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 200.7, 171.4, 171.3, 155.1, 147.5, 140.6, 138.0, 134.3, 134.2, 130.4, 129.8, 129.1, 128.5, 128.1, 128.0, 127.9, 127.5, 127.2, 62.3, 58.6, 53.3, 53.2, 40.9, 39.8, 28.6, 9.4. IR (CH_2Cl_2, cm^{-1}): 2956, 1736, 1655, 1594, 1492, 1441, 1265, 1204, 1075. HRMS (ESI) calcd for $C_{33}H_{30}O_5Na$ $[M+Na]^+$ 529.1991, found 529.2004.

Dimethyl 5-ethyl-6-oxo-5-phenyl-5,6-dihydro-1H-

indene-2,2(3H)-dicarboxylate (**42**)

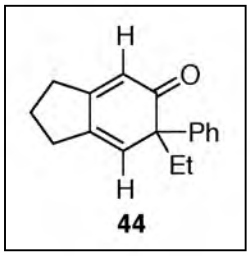


42

The general procedure was used with 39.3 mg (0.18 mmol, 0.1 M) of diyne **41**, 33.1 mg (0.22 mmol) of ketene **33**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford the title compound **42** as slightly yellow oil, 54% yield.

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.25 (m, 5H), 6.25 (s, 1H), 5.95 (s, 1H), 4.24 (m, 4H), 3.30 (m, 4H), 2.50 (dq, J = 4.5 Hz, 1H), 1.91 (dq, J = 4.5 Hz, 1H), 1.27 (m, 6H), 0.78 (t, J = 4.5 Hz, 3H); ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 202.8, 170.7, 159.8, 140.9, 137.1, 135.0, 128.8, 127.4, 127.0, 119.5, 62.2, 59.2, 58.5, 40.3, 38.4, 32.0, 14.2, 9.4. IR (CH_2Cl_2, cm^{-1}): 2975, 1732, 1649, 1446, 1368, 1251, 1190, 1069, 860, 697. HRMS (ESI) calcd for $C_{23}H_{26}O_5Na$ $[M+Na]^+$ 405.1678, found 405.1692.

6-Ethyl-6-phenyl-2,3-dihydro-1H-inden-5(6H)-one (**44**)



44

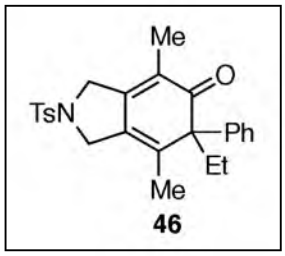
The general procedure was used with 37.0 mg (0.40 mmol, 0.1 M) of diyne **43**, 70.4 mg (0.48 mmol) of ketene **33**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 5-10% ethyl acetate in hexanes to afford the title compound **44** as slightly yellow oil, 35% yield.

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.26 (m, 5H), 6.23 (s, 1H), 5.95 (s, 1H), 2.68 (m, 4H), 2.47 (dq, J = 7.5 Hz, 1H), 1.94 (m, 3H), 0.81 (t, J = 7.5, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 203.6, 164.5, 141.6, 138.3, 135.9, 128.7, 127.2, 127.1, 119.0, 58.4, 33.5, 32.1, 30.8, 24.9, 9.4. IR (CH_2Cl_2, cm^{-1}): 2964, 1675, 1646, 1597, 1492, 1444, 1369, 1301,

1221, 1168, 1034, 857, 758, 696. HRMS (ESI) calcd for $C_{17}H_{18}ONa$ $[M+Na]^+$ 261.1255, found 261.1270.

6-Ethyl-4,7-dimethyl-6-phenyl-2-tosyl-2,3-dihydro-1H-isoindol-5(6H)-one (**46**)

The general procedure was used with 49.1 mg (0.18 mmol, 0.1 M) of diyne **45**, 31.3 mg (0.22 mmol) of ketene **33**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15-30% ethyl acetate in hexanes to afford the title compound **46** as a white solid, 50% yield.



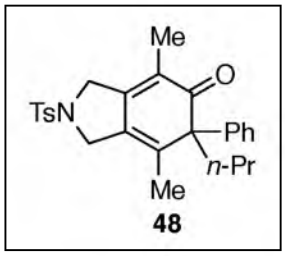
46

Melting Point: 155-158 °C (Decomp.).

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.80 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.21 (m, 3H), 7.05 (m, 2H), 4.31 (s, 2H), 4.25 (d, J = 10.8 Hz, 2H), 2.61 (dq, J = 7.2 Hz, 14.7 Hz, 1H), 2.45 (s, 3H), 1.94 (dq, J =7.2 Hz, 14.7 Hz, 1H), 1.72 (s, 3H), 1.57 (s, 3H), 0.58 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 202.7, 150.0, 144.4, 142.8, 140.8, 133.2, 130.2, 128.99, 128.95, 127.9, 127.4, 126.7, 123.8, 61.6, 52.0, 50.9, 30.0, 21.8, 16.5, 11.5, 8.9. IR (CH_2Cl_2, cm^{-1}): 2926, 1651, 1619, 1493, 1448, 1346, 1272, 1164, 1096, 1061. HRMS (ESI) calcd for $C_{25}H_{27}NO_3SK$ $[M+K]^+$ 460.1349, found 460.1355.

4,7-dimethyl-6-phenyl-6-propyl-2-tosyl-2,3-dihydro-1H-isoindol-5(6H)-one (**48**)

The general procedure was used with 50.6 mg (0.18 mmol, 0.1 M) of diyne **45**, 35.4 mg (0.22 mmol) of ketene **47**, and 5 mol % of catalyst in toluene. The reaction mixture was purified



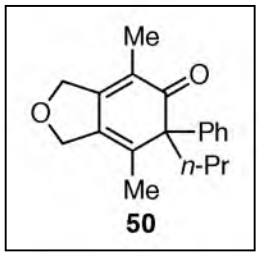
48

via flash column chromatography using 15-30% ethyl acetate in hexanes to afford the title compound **48** as white solid, 55% yield.

Melting Point: 157-160 °C (Decomp.). ^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.81 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.22 (m, 3H), 7.07 (m, 2H), 4.24 (m, 4H), 2.55 (m, 1H), 2.48 (s, 3H), 1.88 (m, 1H), 1.73 (s, 3H), 1.58 (s, 3H), 0.87 (m, 5H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 202.6, 149.9, 144.4, 143.2, 140.9, 135.4, 133.4, 130.2, 129.0, 128.7, 128.0, 127.5, 126.8, 123.6, 61.2, 52.0, 50.9, 39.5, 21.8, 17.9, 16.6, 14.7, 11.5. IR (CH_2Cl_2, cm^{-1}): 2981, 2936, 1734, 1644, 1511, 1447, 1369, 1269, 1206, 1094, 1048, 914. HRMS (ESI) calcd for $C_{26}H_{29}O_3SNa$ $[M+Na]^+$ 458.1766, found 458.1786.

6-Ethyl-4,7-dimethyl-6-phenyl-3,6-dihydroisobenzofuran-5(1H)-one (**50**)

The general procedure was used with 74.2 mg (0.60 mmol, 0.1 M) of diyne **49**, 106.5 mg (0.72 mmol) of ketene **33**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 5-30% ethyl acetate in hexanes to afford the title compound **50** as yellow sticky oil, 33% yield.

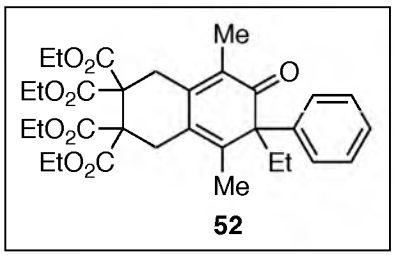


50

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.22 (m, 5H), 4.78 (m, 4H), 2.67 (dq, *J* =4.5 Hz, 1H), 2.00 (dq, *J* =4.5 Hz, 1H), 1.76 (s, 3H), 1.60 (s, 3H), 0.70 (t, *J* =4.5 Hz, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 203.4, 153.8, 141.3, 140.2, 132.0, 128.9, 127.3, 126.9, 121.7, 71.5, 71.0, 61.4, 29.9, 16.5, 11.6, 8.9. IR (CH_2Cl_2, cm^{-1}): 2919, 1653, 1623, 1446, 1054, 698. HRMS (ESI) calcd for $C_{18}H_{20}O_2Na$ $[M+Na]^+$ 291.1361, found 291.1374.

Tetraethyl 6-ethyl-5,8-dimethyl-7-oxo-6-phenyl-6,7-dihydronaphthalene-2,2,3,3(1H,4H)-tetracatboxylate (**52**)

The general procedure was used with 55.3 mg (0.13 mmol, 0.1 M) of diyne **51**, 22.9 mg (0.16 mmol) of ketene **33**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford the title compound **52** as bright yellow sticky oil, 91% yield.

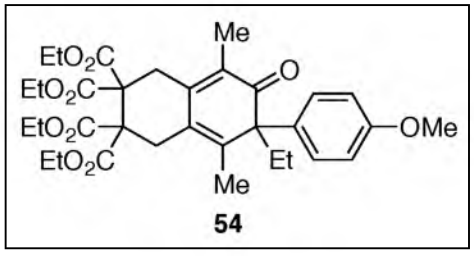


52

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.21-7.09 (m, 5H), 4.27-4.19 (m, 8H), 3.24 (s, 2H), 3.19 (d, J = 11.1 Hz, 2H), 2.65 (dq, J =7.2 Hz, 14.5 Hz, 1H), 1.90 (dq, J=7.2 Hz, 14.5 Hz, 3H), 1.81 (s, 3H), 1.61 (s, 3H), 1.26 (m, J = 7.2 Hz, 12H), 0.62 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 202.0, 170.0, 169.9, 169.8, 169.7, 147.0, 145.6, 141.5, 128.8, 127.1, 127.0, 126.9, 125.3, 62.26, 62.23, 62.21, 61.6, 57.6, 57.2, 34.3, 32.3, 30.3, 16.6, 13.99, 13.98, 13.95, 10.7, 8.7. IR (CH_2Cl_2, cm^{-1}):2981, 1732, 1645, 1446, 1368, 1268, 1205, 1048. HRMS (ESI) calcd for $C_{32}H_{40}O_9Na$ $[M+Na]^+$ 591.2570, found 591.2586.

Tetraethyl 6-ethyl-6-(4-methoxyphenyl)-5,8-dimethyl-7-oxo-6,7-dihydronaphthalene-2,2,3,3(1H,4H)-tetracarboxylate (**54**)

The general procedure was used with 54.1 mg (0.13 mmol, 0.1 M) of diyne **51**, 27.06 mg (0.15 mmol) of ketene **53**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford the title compound **54** as bright yellow sticky oil, 81% yield.

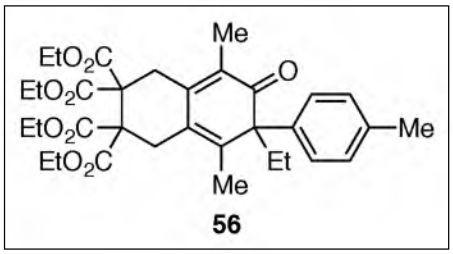


54

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.05 (d, *J* = 9Hz, 2H), 6.77 (d, *J* = 9 Hz, 2H), 4.25 (m, 8H), 3.75 (s, 3H), 3.26 (s, 2H), 3.21 (d, *J* = 12 Hz, 2H), 2.63 (dq, *J* =7.2 Hz, 15 Hz, 1H), 1.94 (dq, *J* =7.2 Hz, 14.5 Hz, 1H), 1.83 (s, 3H), 1.64 (s, 3H), 1.28 (m, 12H), 0.63 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 202.4, 170.0, 169.89, 169.84, 169.8, 158.6, 146.8, 145.8, 133.5, 127.9, 127.0, 125.1, 114.2, 62.29, 62.26, 60.9, 57.6, 57.2, 55.4, 34.3, 32.2, 30.4, 16.6, 14.0, 10.7, 8.8. IR (CH_2Cl_2, cm^{-1}): 2981, 1732, 1644, 1447, 1369, 1460, 1368, 1250, 1205, 1093, 1036. HRMS (ESI) calcd for $C_{33}H_{42}O_{10}Na$ $[M+Na]^+$ 621.2676, found 621.2689.

Tetraethyl 6-ethyl-5,8-dimethyl-7-oxo-6-(p-tolyl)-6,7-dihydronaphthalene-2,2,3,3(1H,4H)-tetracarboxylate (**56**)

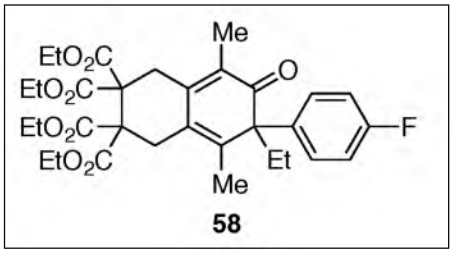
The general procedure was used with 46.4 mg (0.11 mmol, 0.1 M) of diyne **51**, 20.8 mg (0.13 mmol) of ketene **55**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford the title compound **56** as bright yellow sticky oil, 80% yield.



56

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.03 (d, *J* = 3Hz, 4H), 4.26 (m, 8H), 3.26 (s, 4H), 2.66 (dq, *J* = 7.2 Hz, 14.7 Hz, 1H), 2.42 (s, 3H), 1.96 (dq, *J* = 7.5 Hz, 14.8 Hz, 1H), 1.83 (s, 3H), 1.65 (s, 3H), 1.29 (m, 12H), 0.64 (t, *J* = 7.2Hz, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 202.3, 170.0, 169.9, 169.89, 169.8, 146.9, 145.8, 138.5, 136.8, 129.6, 127.0, 126.8, 125.2, 62.3, 62.28, 61.2, 57.6, 57.2, 34.3, 30.3, 21.2, 16.6, 14.05, 14.05, 14.03, 14.01, 10.8, 8.8. IR (CH_2Cl_2, cm^{-1}): 2982, 2935, 1733, 1644, 1269, 1206, 1049, 1048. HRMS (ESI) calcd for $C_{33}H_{42}O_9Na$ $[M+Na]^+$ 605.2727, found 605.2733.

Preparation of tetraethyl 6-ethyl-6-(4-fluorophenyl)-5,8-dimethyl-7-oxo-6,7-dihydronaphthalene-2,2,3,3(1H,4H)-tetracarboxylate (**58**)

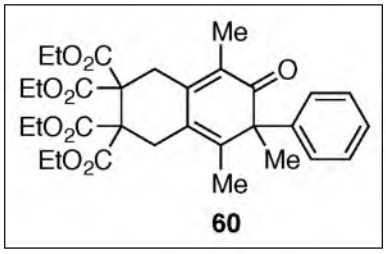


58

The general procedure was used with 50 mg (0.118 mmol, 0.1 M) of diyne **51**, 23.4 mg (0.14 mmol) of ketene **57**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford the title compound **58** as bright yellow sticky oil, >99% yield.

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.11 (m, *2*H), 6.93 (m, 2H), 4.28 (m, 8H), 3.23 (m, 4H), 2.63 (dq, *J* = 7.2 Hz, 1H), 1.95 (dq, *J* = 7.5 Hz, 1H), 1.84 (s, 3H), 1.63 (s, 3H), 1.29 (m, 12H), 0.64 (t, *J* = 7.5Hz, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 201.9, 170.0, 169.9, 169.76, 169.7, 163.5, 160.3, 147.1, 145.2, 137.2, 128.6, 128.5, 127.1, 125.5, 115.8, 115.5, 62.3, 60.9, 57.6, 57.1, 34.3, 32.2, 30.6, 16.5, 14.0, 10.7, 8.7. IR (CH_2Cl_2, cm^{-1}): 2983, 2938, 1748, 1644, 1269, 1206, 1055, 1048. HRMS (ESI) calcd for $C_{32}H_{39}O_9FNa$ $[M+Na]^+$ 609.2476, found 609.2477.

Tetraethyl 5,6,8-trimethyl-7-oxo-6-phenyl-6,7-dihydronaphthalene-2,2,3,3(1H,4H)-tetracarboxylate (**60**)



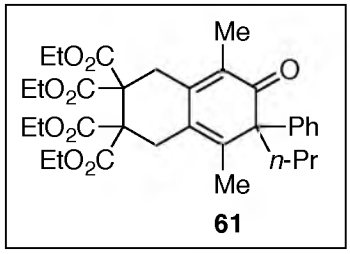
60

The general procedure was used with 100 mg (0.24 mmol, 0.1 M) of diyne **51**, 37.4 mg (0.28 mmol) of ketene **59**, and 5 mol % of catalyst, in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford the title compound **60** as bright yellow sticky oil, 65%.

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.23 (m, 3H), 7.12 (m, 2H), 4.26 (m, 8H), 3.27 (s, 2H), 3.18 (m, 2H), 1.84 (s, 3H), 1.65 (s, 3H), 1.60 (s, 3H), 1.27 (m, 12H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 202.0, 169.9, 169.8, 169.78, 146.8, 146.5, 141.4, 128.7, 127.0, 126.8, 125.9, 122.9, 62.2, 62.1, 57.6, 57.2, 56.9, 34.3, 32.2, 30.4, 29.8, 22.8, 17.0, 13.9, 10.9. IR (CH_2Cl_2, cm^{-1}): 2983, 1732, 1647, 1445, 1367, 1269, 1205, 1094, 1038. HRMS (ESI) calcd for $C_{31}H_{38}O_9Na$ $[M+Na]^+$ 577.2414, found 577.2419.

Tetraethyl 5,8-dimethyl-7-oxo-6-phenyl-6-propyl-6,7-dihydronaphthalene-2,2,3,3(1H,4H)-tetracarboxylate (**61**)

The general procedure was used with 209.1 mg (0.49 mmol, 0.1 M) of diyne **51**, 95.0 mg (0.59 mmol) of ketene **47**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford the title compound **61** as bright yellow sticky oil, 76% yield.

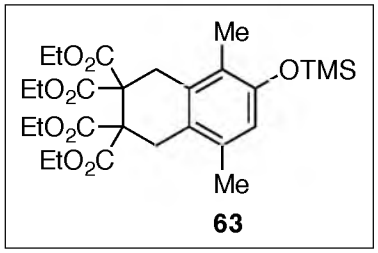


61

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.19 (m, 5H), 4.25 (m, 8H), 3.18 (m, 4H), 2.59 (m, 1H), 1.91 (m, 1H), 1.82 (s, 3H), 1.62 (s, 3H), 1.27 (m, 12H), 0.97 (m, 2H), 0.85 (m, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 202.0, 170.0, 169.86, 169.82, 169.8, 146.8, 146.0, 141.5, 128.8, 128.7, 127.1, 126.8, 124.8, 62.3, 62.2, 61.2, 57.6, 57.3, 39.7, 34.3, 32.1, 17.6, 16.7, 14.7, 14.0, 10.7. IR (CH_2Cl_2, cm^{-1}): 2982, 1735, 1646, 1446, 1368, 1267, 1208, 1096, 1033. HRMS (ESI) calcd for $C_{33}H_{42}O_9Na$ $[M+Na]^+$ 605.2727, found 605.2726.

Tetraethyl 5,8-dimethyl-6-((trimethylsilyl)oxy)naphthalene-2,2,3,3(1H,4H)-tetracarboxylate (**63**)

The general procedure was used with 104.5 mg (0.25 mmol, 0.1 M) of diyne **51**, 41.7 mg (0.30 mmol) of ketene **62**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 10-15% ethyl acetate in hexanes to afford the title compound **63** as colorless oil, 63% yield.

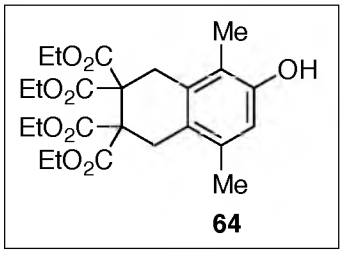


63

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 6.45 (s, 1H), 4.15 (m, 8H), 3.33 (s, 2H), 3.25 (s, 2H), 2.15 (s, 3H), 2.05 (s, 3H), 1.16 (t, J_1= 7.2 Hz, 12H), 0.19 (s, 9H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 193.7, 170.4, 170.36, 151.0, 133.5, 132.7, 124.3, 123.5, 119.1, 76.1, 61.84, 61.8, 57.612, 57.3, 33.3, 32.4, 19.8, 13.9, 12.0, 7.9, 0.6. IR (CH_2Cl_2, cm^{-1}): 2982, 1736, 1579, 1475, 1367, 1257, 1203, 1096, 1052, 913, 843. HRMS (ESI) calcd for $C_{27}H_{40}O_9SiNa$ $[M+Na]^+$ 559.2339, found 559.2340.

Tetraethyl 6-hydroxy-5,8-dimethylnaphthalene-2,2,3,3(1H,4H)-tetracarboxylate (**64**)[15]

On eluting the column with 15-20% ethyl acetate in hexanes the title compound **64** was obtained as a white solid, 19% yield.[15] Melting Point: 120-123 °C (Lit:[3] 121.5-122 °C).

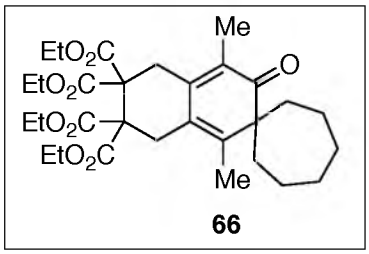


64

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 6.41 (s, 1H), 5.29 (s, 1H), 4.19 (m, 8H), 3.36 (s, 2H), 3.29 (s, 2H), 2.12 (s, 3H), 2.07 (s, 3H), 1.21 (t, J= 7.2 Hz, 12H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 170.5, 170.4, 151.6, 133.7, 132.4, 123.2, 118.8, 115.2, 61.99, 61.95, 57.5, 57.3, 33.2, 32.4, 19.6, 13.9, 11.0. IR (CH_2Cl_2, cm^{-1}): 3452, 2983, 1733, 1463, 1270,

1205, 1085, 1052. HRMS (ESI) calcd for $C_{24}H_{32}O_9Na$ $[M+Na]^+$ 487.1944, found 487.1953.

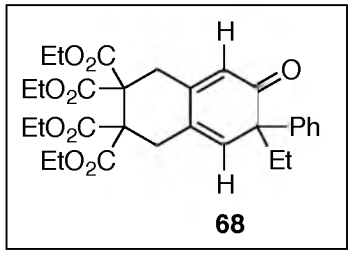
Tetraethyl 1',4'-dimethyl-3'-oxo-3'H-spiro[cycloheptane-1,2'-naphthalene]-6',6',7',7'(5'H,8'H)-tetracarboxylate (**66**)



66

The general procedure was used with 40.2 mg (0.095 mmol, 0.1 M) of diyne **51**, 14.1 mg (0.11 mmol) of ketene **65**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford the title compound **66** as pale oil, 76% yield. ^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 4.20 (m, 8H), 3.15 (s, 2H), 3.04 (s, 2H), 1.91 (s, 3H), 1.86 (s, 3H), 1.59 (m, 12H), 1.25 (m, 12H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 204.2, 169.96, 169.93, 149.0, 143.6, 125.8, 120.6, 62.2, 62.1, 57.7, 57.6, 57.2, 35.2, 33.9, 32.2, 31.9, 29.8, 24.9, 15.8, 14.02, 14.00, 11.4. IR (CH_2Cl_2, cm^{-1}): 2956, 1736, 1648, 1437, 1263, 1204, 1076. HRMS (ESI) calcd for $C_{31}H_{38}O_9Na$ $[M+Na]^+$ 569.2727, found 569.2737.

Tetraethyl 6-ethyl-7-oxo-6-phenyl-6,7-dihydronaphthalene-2,2,3,3(1H,4H)-tetracarboxylate (**68**)

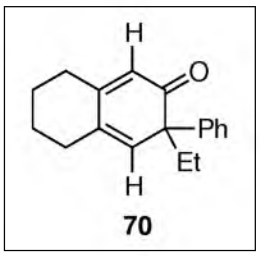


68

The general procedure was used with 48.2 mg (0.12 mmol, 0.1 M) of diyne **67**, 21.4 mg (0.14 mmol) of ketene **33**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford the title compound **68** as yellow sticky oil, 78% yield.

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.24 (m, 5H), 6.21 (s, 1H), 5.85 (s, 1H), 4.23 (m, 8H), 3.30 (m, 4H), 2.48 (dq, *J* = 7.2 Hz, 1H), 1.90 (dq, *J* = 7.2 Hz, 1H), 1.27 (m, 12H), 0.78 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 202.3, 169.56, 169.5, 169.4, 169.3, 151.7, 141.6, 140.5, 128.8, 128.2, 127.4, 126.9, 123.0, 62.4, 62.34, 62.31, 58.9, 58.2, 57.3, 35.4, 34.2, 31.8, 14.0, 9.4. IR (CH_2Cl_2, cm^{-1}): 2981, 1733, 1662, 1445, 1367, 1268, 1093, 1044, 863, 689. HRMS (ESI) calcd for $C_{30}H_{36}O_9Na$ $[M+Na]^+$ 563.2257, found 563.2253.

3-Ethyl-3-phenyl-5,6,7,8-tetrahydronaphthalen-2(3H)-one (**70**)



70

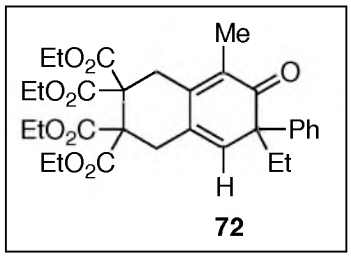
The general procedure was used with 42.9 mg (0.40 mmol, 0.1 M) of diyne **69**, 70.8 mg (0.48 mmol) of ketene **33**, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 5-10% ethyl acetate in hexanes to afford the title compound **70** as bright yellow oil, 33% yield.

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.26 (m, 5H), 6.14(s, 1H), 5.80 (s, 1H), 2.58 (m, 4H), 2.45 (dq, *J* = 7.5 Hz, 1H), 1.93 (dq, *J* = 7.5 Hz, 1H), 1.75 (m, 4H), 0.81(t, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 203.2, 157.0, 141.2, 140.37, 132.4, 128.7, 127.2, 127.1, 122.9, 58.5, 32.1, 30.8, 29.1, 23.1, 22.1, 9.5. IR (CH_2Cl_2, cm^{-1}): 2934, 1658, 1492, 1448, 1382, 1231, 853, 764, 697. HRMS (ESI) calcd for $C_{18}H_{20}ONa$ $[M+Na]^+$ 275.1412, found 275.1419.

Tetraethyl 7-ethyl-5-methyl-6-oxo-7-phenyl-6,7-dihydronaphthalene-2,2,3,3(1H,4H)-tetracarboxylate (**72**)

The general procedure was used with 50.7 mg (0.12 mmol, 0.1 M) of diyne **71**, 21.7 mg (0.14 mmol) of ketene **33**, and 5 mol % of catalyst in toluene. The reaction mixture

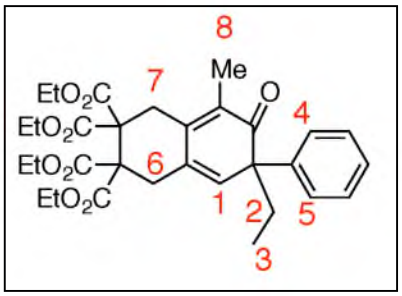
was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford the title compound **72** as yellow sticky oil, 66% yield.



72

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.25 (m, 5H), 6.12 (s, 1H), 4.25 (m, 8H), 3.30 (m, 4H), 2.48 (dq, *J* = 7.2 Hz, 1H), 1.90 (dq, *J* = 7.2 Hz, 1H), 1.83 (s, 3H), 1.28 (m, 12H), 0.75 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 202.0, 169.9, 169.6, 169.5, 145.2, 140.9, 138.5, 128.9, 128.3, 128.1, 127.3, 127.0, 62.3, 62.2, 57.68, 57.62, 57.5, 34.8, 34.0, 32.1, 14.0, 10.9, 9.4. IR (CH_2Cl_2, cm^{-1}): 2981, 1733, 1645, 1445, 1368, 1269, 1092, 1044, 914, 863, 689. HRMS (ESI) calcd for $C_{31}H_{38}O_9Na$ $[M+Na]^+$ 577.2414, found 577.2411.

Regioselectivity was assigned on the basis of (a). nOe of proton on C-1 with protons on C-2 (only one H), C-3, C-4, C-5, and C6; (b). nOe of proton on C-8 with protons on C-7.



General procedure for the asymmetric cycloaddition

In a nitrogen-filled glove box, a 5 mol % catalyst solution (prepared from $Ni(COD)_2$ and (*R*)-BINAP in 1:1 molar ratio in toluene) was added to the solution of 55.3 mg (0.13 mmol) of diyne **51**, 22.9 mg (0.16 mmol) of ketene **33**. The resulting reaction mixture was then stirred at 80 °C for 5 h or 100 °C for 12 h, opened to air, and concentrated *in vacuo*. The remaining residue was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford the title compound **52*** as bright yellow sticky oil, 38% (99% *ee* @ 80 °C) and 58% (95% ee @ 100 °C) yields. SFC (supercritical fluid

chromatography) analysis was performed at 40 °C, using a Thar instrument fitted with a chiral stationary phase (Cellucoat).

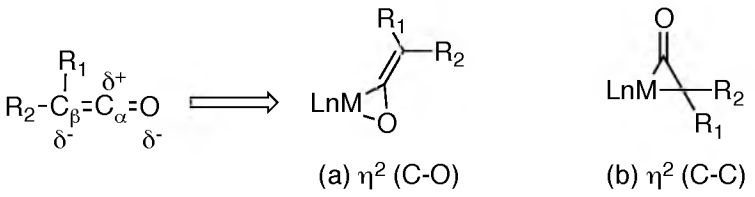
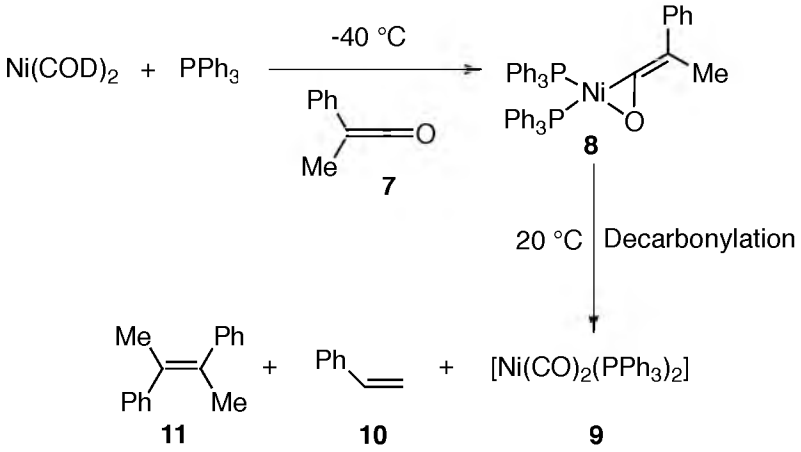
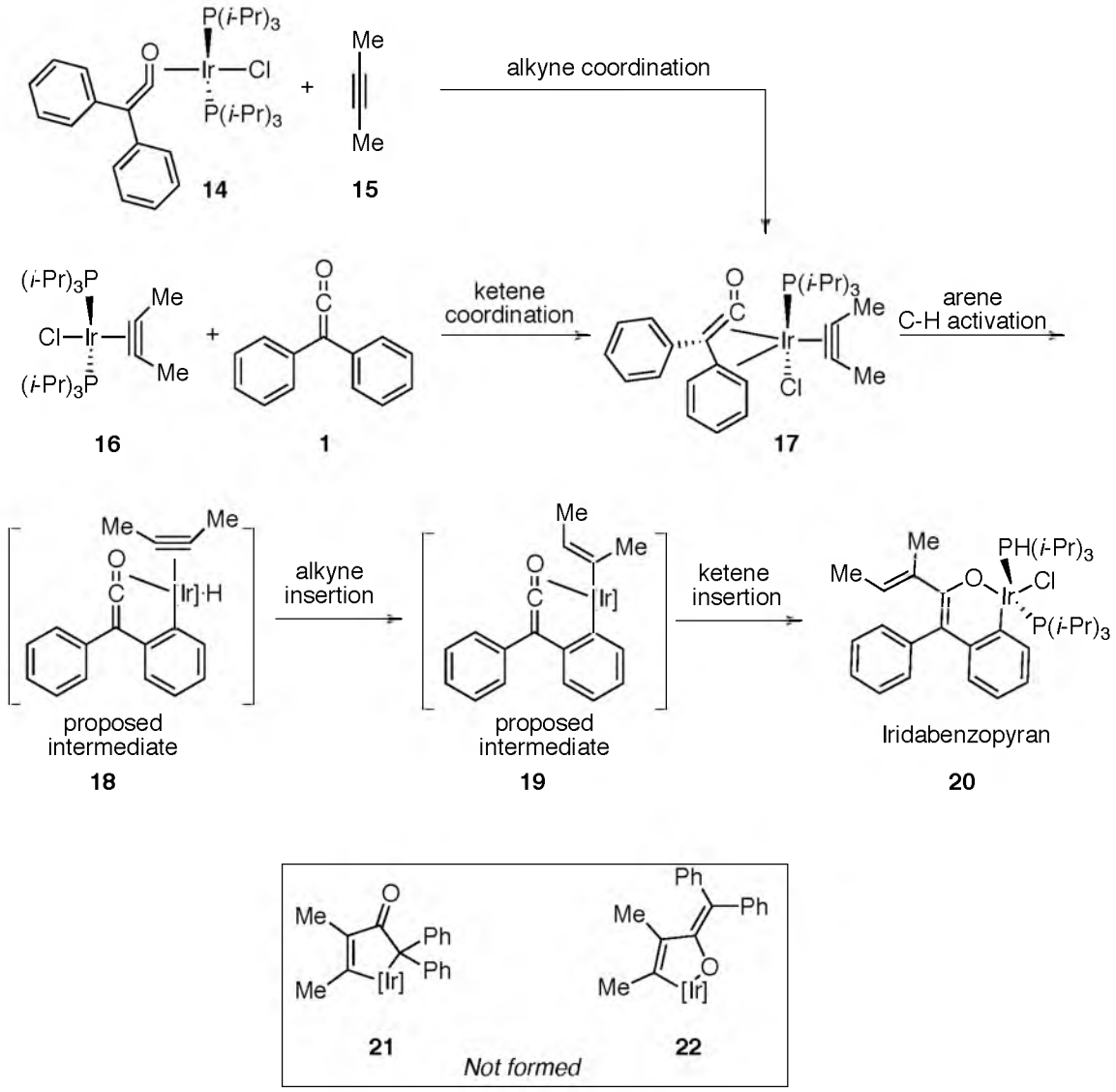


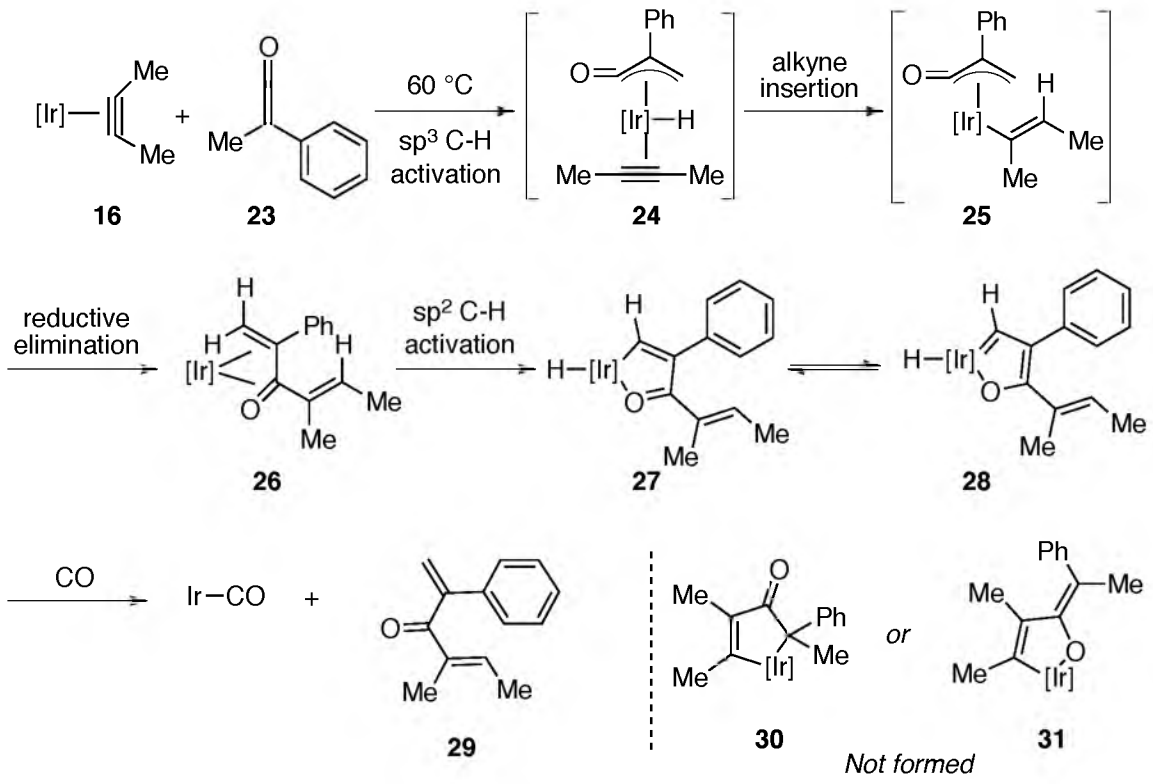
Figure 1.1. Modes of ketene coordination



Scheme 1.1 Decarbonylation of nickel-ketene complex



Scheme 1.2 Ketene-alkyne complex of iridium



Scheme 1.3 Reaction of iridium-alkyne complex with ketene

Table 1.1 Screening of N-heterocyclic carbenes

Entry	Ligand	% Conv.[a]	% Yield[a]
1	IPr	>99	12
2	SIPr	63	3
3	IMes	>99	7
4	SIBen	57	2
5	I*i*Pr	57	7

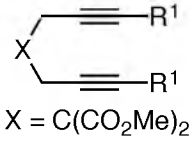
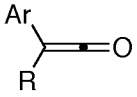
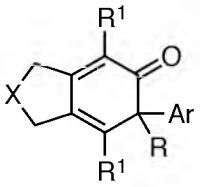
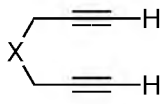
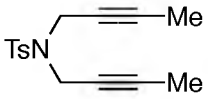
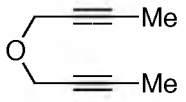
[a]Analyzed by GC using decane as an internal standard

Table 1.2 Screening of monodentate and bidentate phosphines[a]

Entry	Ligand (L_n)	Ni:L_n	% Conv.[b]	% Yield[b]
1	PPh_3	1:2	>99	39
2	P(*o*-Tol)$_3$	1:2	54	2
3	PCy_3	1:2	>99	20
4	P*n*-Bu_3	1:2	52	10
5	PEt_3	1:2	62	17
6	$MePPh_2$	1:2	>99	54
7	$CyPPh_2$	1:2	>99	31
8	DPPE	1:1	32	2
9	DCPE	1:1	22	-
10	**DPPB**	1:1	**>99**	86 (**86**)[c]
11	**DPPF**	1:1	**>99**	>99 (**86**)[c]

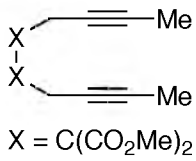
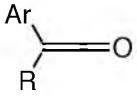
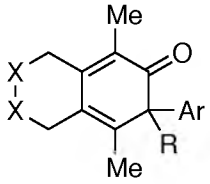
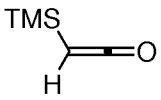
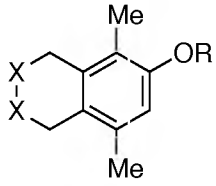
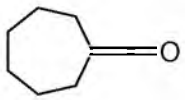
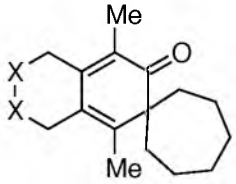
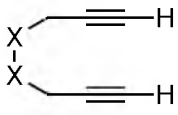
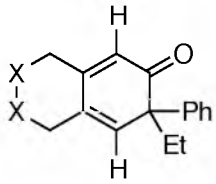
[a] Reaction conditions: Ni-catalyst (5 mol %), diyne (1 equiv), and ketene (1.2 equiv) in benzene at 60 °C for 12 h. [b] Analyzed by GC using decane as an internal standard. [c] The value in parentheses are isolated yields.

Table 1.3 Ni-catalyzed cycloaddition of diynes and ketenes[a]

Entry	Diyne	Ketene	Product	Yield[b,c]
	 X = $C(CO_2Me)_2$			
1	**32** (R^1 = Me)	**33** Ar = Ph, R = Et	**34**	82 %
2	**32**	**35** Ar = Ph, R = Ph	**36**	46 %
3	**32**	**37** Ar = Ph, R = *i*-Pr	**38**	50 %
4	**39** (R^1 = Ph)	**33** Ar = Ph, R = Et	**40**	65 %
				
5	**41** (X = $C(CO_2Et)_2$	**33** Ar = Ph, R = Et	**42**	54 %
6	**43** (X = CH_2)	**33** Ar = Ph, R = Et	**44**	35 %
				
7	**45**	**33** Ar = Ph, R = Et	**46**	50 %
8	**45**	**47** Ar = Ph, R = *n*-Pr	**48**	55 %
				
9	**49**	**33** Ar = Ph, R = Et	**50**	33 %

[a] Reaction conditions: $Ni(COD)_2$ (5 mol %), DPPB (5 mol %), diyne (1 equiv, 0.1 M), and ketene (1.2 equiv) in toluene at 60 °C for 5 h. [b] Isolated yields. [c] Average of two runs.

Table 1.4 Ni-catalyzed cycloaddition of diynes and ketenes[a]

Entry	Diyne	Ketene	Product	Yield[b,c]
	 X = $C(CO_2Me)_2$			
1	**51**	**33** Ar = Ph, R = Et	**52**	91 %
2	**51**	**53** Ar = *p*-OMe-Ph, R = Et	**54**	81 %
3	**51**	**55** Ar = *p*-Me-Ph, R = Et	**56**	80 %
4	**51**	**57** Ar = *p*-F-Ph, R = Et	**58**	>99 %[d]
5	**51**	**59** Ar = Ph, R = Me	**60**	65 %
6	**51**	**47** Ar = Ph, R = *n*-Pr	**61**	76 %
7	**51**	 **62**	 **63-64** R = TMS:H = 63:19	82 %
8	**51**	 **65**	 **66**	76 %
9	 **67** (X = $C(CO_2Et)_2$)	**33**	 **68**	78 %
10	**69** (X = CH_2)	**33**	**70**	33 %

[a] Reaction conditions: $Ni(COD)_2$ (5 mol %), DPPB (5 mol %), diyne (1 equiv, 0.1 M), and ketene (1.2 equiv) in toluene at 60 °C for 5 h. [b] Isolated yields. [c] Average of two runs. [d] Crude ketene was used.

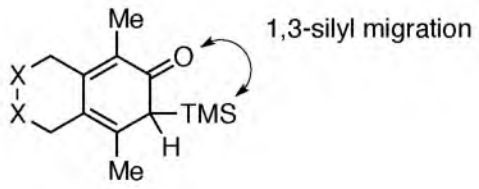
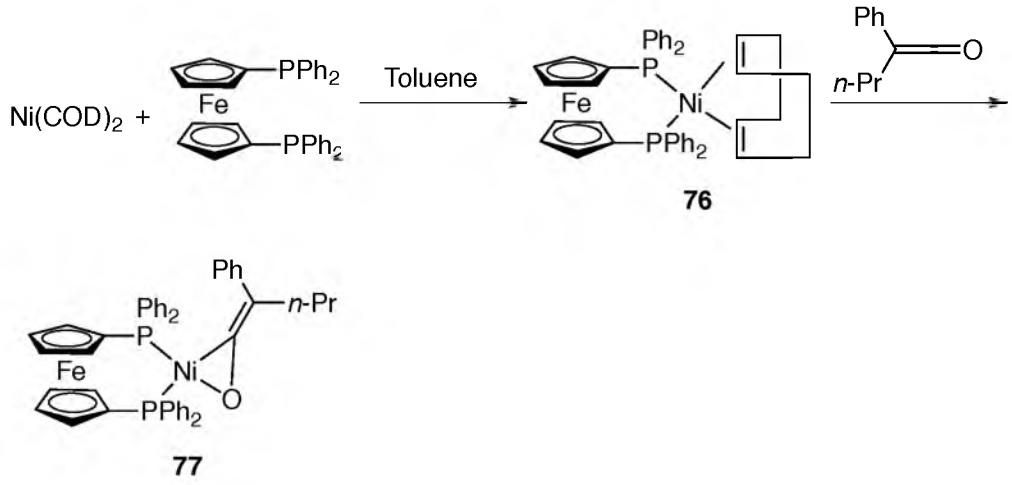
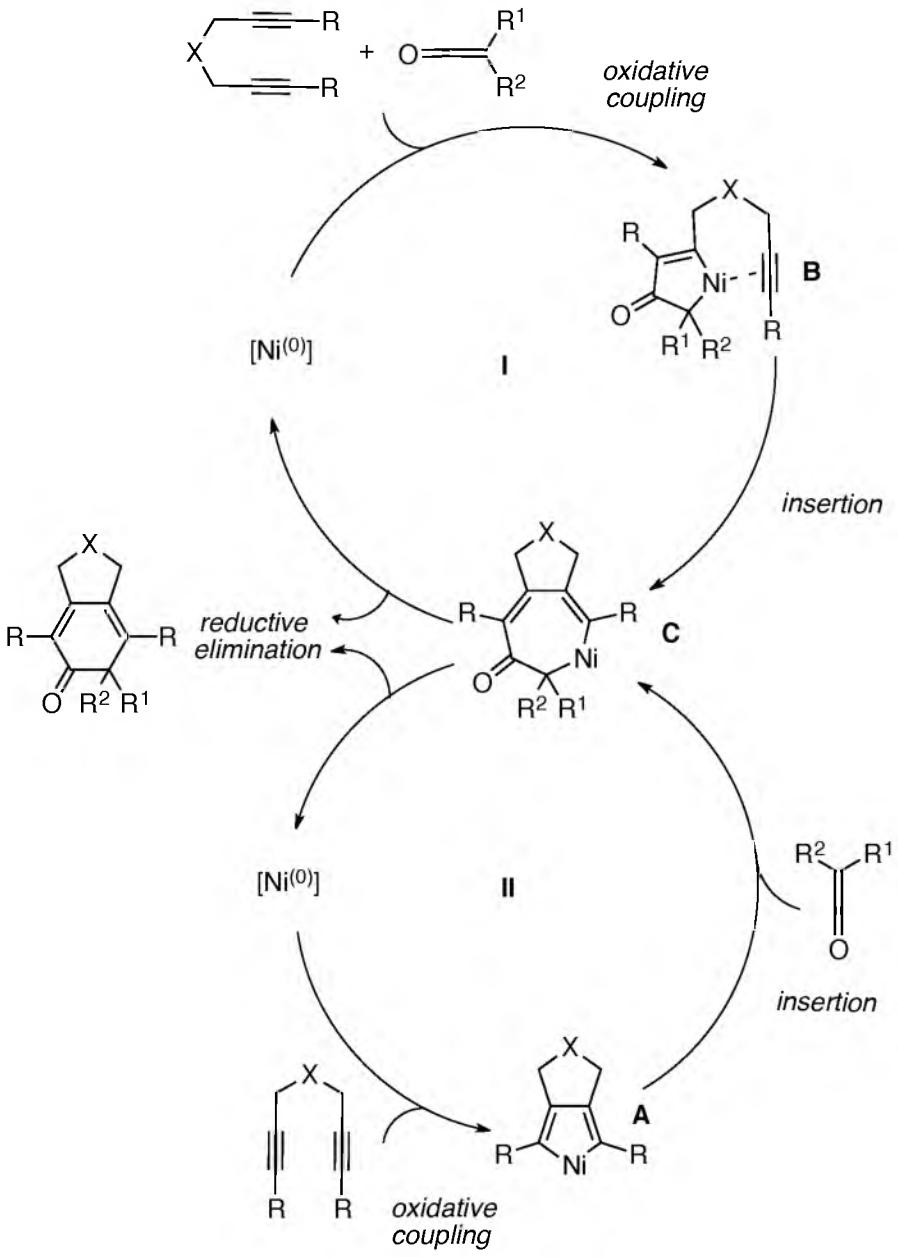


Figure 1.2 Proposed intermediate

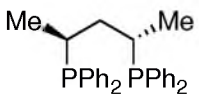
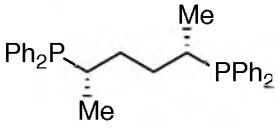
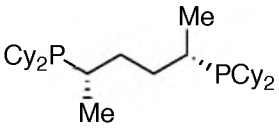
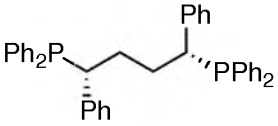
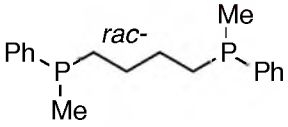
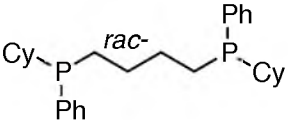


Scheme 1.4 Preparation of stable Ni-ketene complex



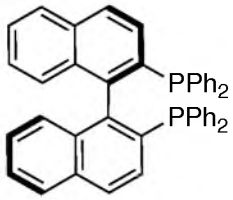
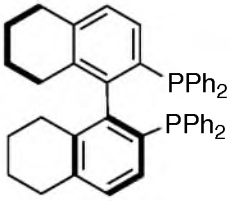
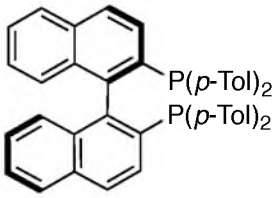
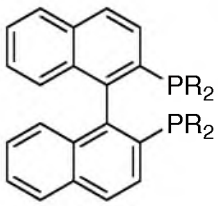
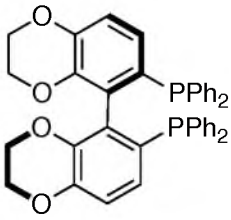
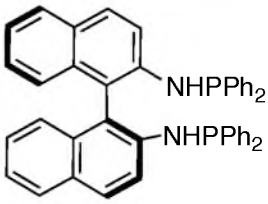
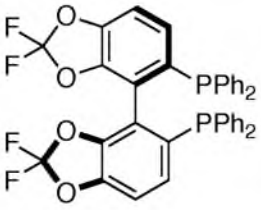
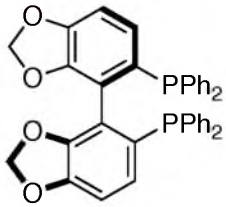
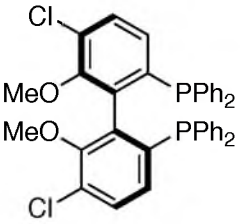
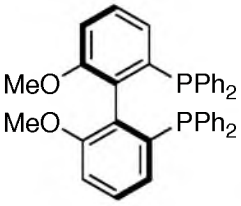
Scheme 1.5 Proposed mechanism

Table 1.5 Nickel-catalyzed asymmetric cycloaddition of diynes and ketenes[a]

		
73 %, 40 %[a]	49 %, nd	No Rxn.
		
50 %, nd	23%	No Rxn.

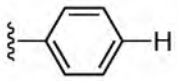
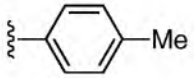
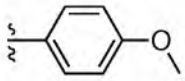
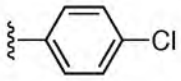
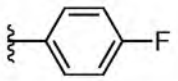
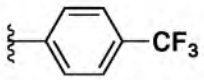
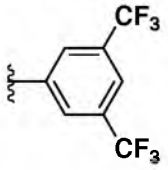
[a]Isolated yields (in black) and enantiomeric excess (in red) determined by chiral SFC

Table 1.6 Ni-catalyzed asymmetric cycloaddition of diynes and ketenes[a]

		
(R)-BINAP	*(S)-H8*-BINAP	*(R)-Tol*-BINAP
38 %, 99 % @80 °C 58 %, 95 % @ 110 °C	43 %, 90 %	55 %, nd
		
R= Cy, i-Pr	*(R)*-SYNPHOS	*(S)-H8*-BINAM-P
No Rxn.	18 %, nd	43 %, nd
		
(R)-DIFLUOROPHOS	*(R)*-SEGPHOS	*(S)*-Cl-OMe-BIPHEP
25 %, nd	No Rxn.	55 %, 87 %
		
	(S)-OMe-BIPHEP	
	50 %, nd	

[a]Isolated yields (in black) and enantiomeric access (in red) determined by chiral SFC

Table 1.7 Effects of electronics on BINAP

Ar =	% Yield
	58
	55
	0
	13
	0
	**70**
	**83**

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CHAPTER 2

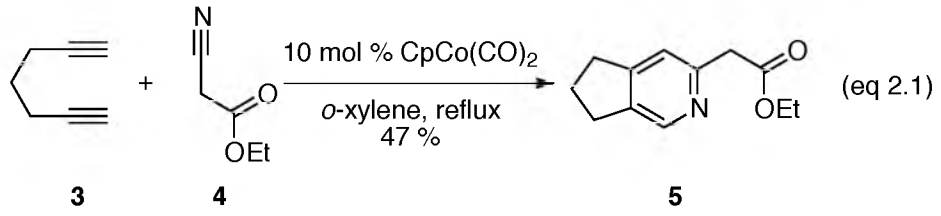
A SERENDIPITOUS DISCOVERY: NICKEL CATALYST FOR THE CYCLOADDITION OF DIYNES WITH UNACTIVATED NITRILES

Introduction

Pyridine, a highly conjugated heteroaromatic compound, has attracted the attention of scientists from various streams of chemistry. Their wide presence in several biologically important natural products and drugs make them an attractive target for organic synthesis.[1] Since the early discovery by Hantzsch on the synthesis of dihydropyridine, immense progress has been made to access a wide variety of pyridine motifs. In particular, co-cyclotrimerization of alkynes and nitriles serves as a very important method by which monocyclic as well as bicyclic pyridines can be easily accessed in a highly atom-economical manner.[2-3]

Specifically, Co-, Ru-, Rh-, Fe-, Ni-, and Ir-based complexes have significantly advanced the metal-catalyzed [2+2+2] cycloaddition of alkynes and nitriles to form pyridines.[4-9] The mechanism of this transformation is still not completely understood however, the existing mechanistic data suggest that most of the catalysts (Co, Ru, Rh, Fe, Ni and Ir) generate pyridines through a mechanism that involves initial oxidative coupling of the alkynes and then subsequent insertion of the nitrile (Scheme 2.1).[10]

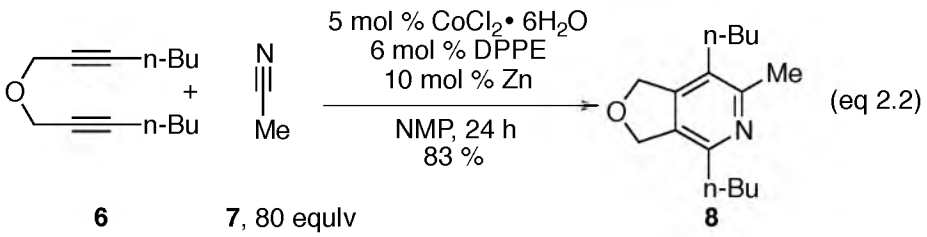
Wakatsuki was the first to realize the feasibility of this concept of coupling two alkynes with a nitrile. The authors prepared and exposed the homo-oxidative coupling product, cobaltacyclopentadiene **2**, to nitriles, which on heating to 70 °C, led to the formation of a pyridine product in fair yields (Scheme 2.2). Volhardt and coworkers made a significant advancement by coupling diynes and nitriles using only catalytic amount of cobalt complex (eq 2.1).



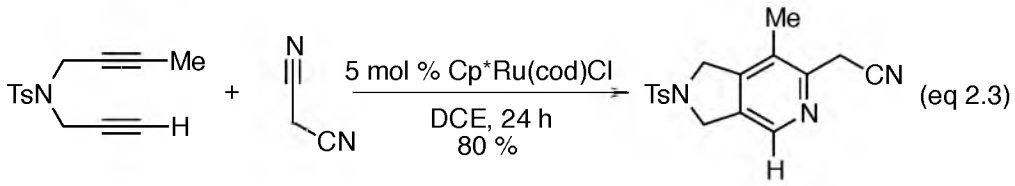
3 **4** **5**

Several studies have been published to improve the catalytic efficiency of Co-catalysts. Okamoto's group reported a more general cobalt catalyst, which enabled the cycloaddition of diynes and nitriles under mild conditions (room temperature to 50 °C) (eq 2.2).[11] However, the reaction required the use of an excess amount of nitrile and prolonged reaction times. Itoh's laboratory has extensively exploited the concept of homo-coupling of alkynes in cyclotrimerization reactions using a Ru-catalyst for the synthesis of carbocyclic compounds. These Ru-complexes also catalyzed the formation of pyridine products over alkyne oligomerization (eq 2.3). The reaction was high yielding and regioselective. However, the catalyst exhibited a unique dependence on nitriles, wherein only alkyl, alkenyl, and aryl nitriles with an additional coordinating group could be used as substrates. The use of acetonitrile or benzonitrile did not lead to any product formation. Similarly, Tanaka's conditions, which employ a Rh-catalyst, enabled the coupling of a wide variety of diynes with not only activated nitriles but also unactivated

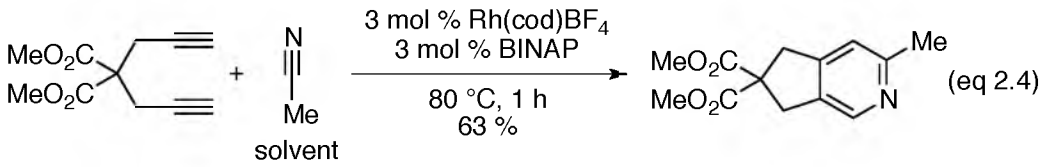
nitriles (eq 2.4). The reaction was general and high yielding, but a large excess of the unactivated nitrile was necessary to achieve high conversions. Very recently, Takeuchi introduced an Ir-based catalyst, which converted diynes and nitriles into pyridine products in high yields.



6 **7**, 80 equlv **8**



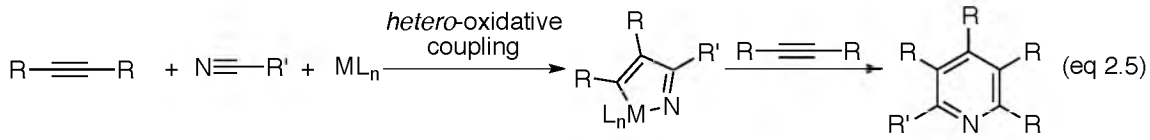
9 **10** **11**



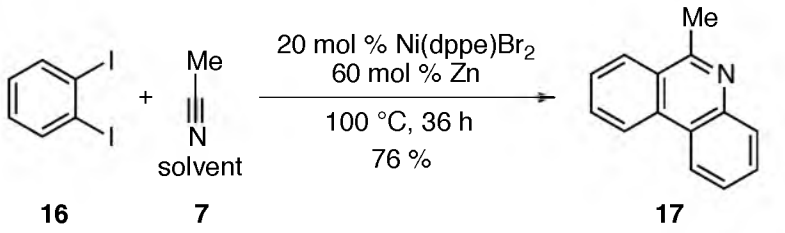
12 **7** **13**

In contrast to previously mentioned catalyst systems, Ni-mediated cycloadditions are thought to undergo hetero-oxidative coupling between a single alkyne and the heteroatom-containing substrate, such as a nitrile, before insertion of the second alkyne (eq 2.5).[12] Thus, a Ni/L_n-based system (especially where L_n = phosphine) that yields pyridines remained absent, because of the difficulty associated with forming the required azametallacyclopentadiene intermediate, until two notable solutions were developed.

Takahashi et al. accessed the azametallacyclopentadiene intermediate **15** *stoichiometrically* through transmetallation between $[Ni(PPh_3)_2Cl_2]$ and an azazirconacyclopentadiene complex **14** (Scheme 2.2). Alternatively, catalytic pyridine formation was achieved at 100 °C between activated alkynes such as benzyne (generated *in-situ* from diiodobenzene precursor **16**) and excess alkyl nitriles such as **7** with Ni/dppe (dppe=1,2-bis(diphenylphosphino)ethane) as the catalyst (eq 2.6).



(eq 2.5)



16 **7** **17**

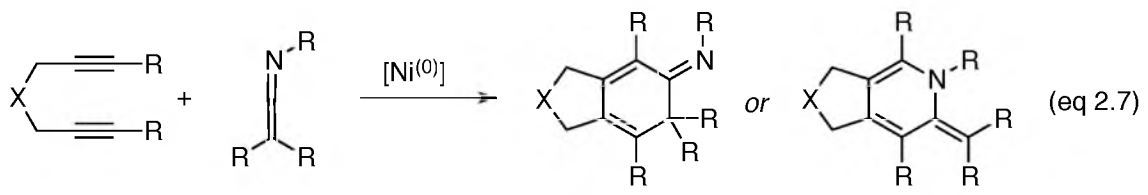
(eq 2.6)

The challenge of incorporating unactivated nitriles in the cycloaddition reaction with diynes in a highly atom-efficient manner was successfully addressed by Louie's laboratory by replacing the phosphines with N-heterocyclic carbene (NHC) ligands. Thus, enhancing the nucleophilicity of the nickel center appeared to be the key for promoting oxidative coupling of the alkyne and nitrile.

Recently, we reported a nickel-catalyzed cycloaddition of diynes and ketenes.[14] In our efforts to expand this chemistry to ketenimines, we serendipitously discovered that the combination of Ni^0 and Xantphos (Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) serves as a general catalyst system for the cycloaddition of diynes and nitriles. Furthermore, these cycloadditions proceed, in many cases, more effectively than the current state-of-the-art catalytic methods.

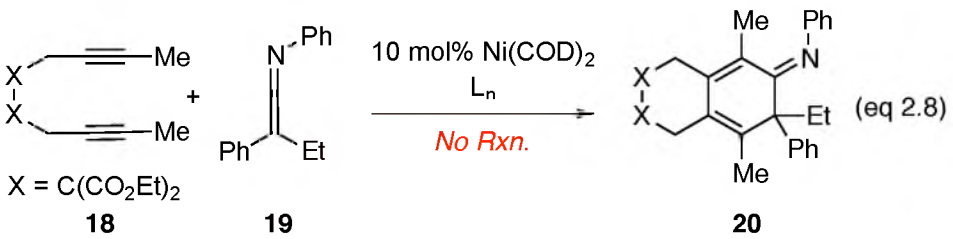
Results and discussion

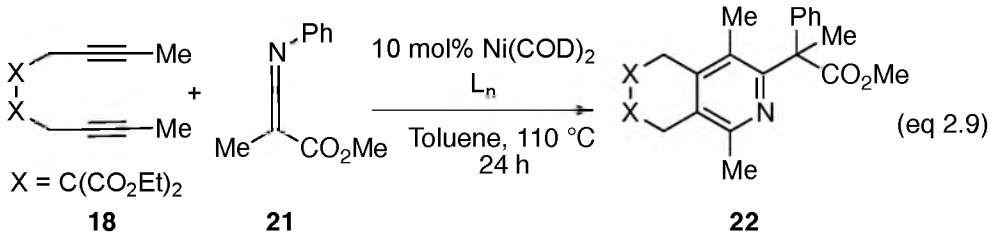
We became interested in nitrogen containing analogs of ketenes, ketinimines that are relatively easier to prepare and more thermally stable than ketenes. Encouraged by this feature of ketinimines, we hoped to expand the scope of our ketene cycloaddition chemistry (eq 2.7). Our initial efforts to incorporate ketenimine **19** in nickel-catalyzed cycloaddition with diyne **18** met with failure as no product formation was detected in case of several NHCs and phosphine ligands investigated in this study (eq 2.8). Therefore, to further enhance ketenimine reactivity, we planned to polarize its electron density by introducing an electron-withdrawing (-CO_2Me) group. Upon investigating reaction conditions to promote the cycloaddition between the diyne **18** and methyl 2-methyl-3-(phenylimino)acrylate **21**, we found that pyridine **22** (rather than the expected carbocycle as illustrated in eq 2.7) was obtained in moderate yield when Xantphos (or P(O*i*-Pr)$_3$) was used as the ligand (eq 2.9 and Table 2.1). Further optimization with either Xantphos or P(O*i*-Pr)$_3$ did not lead to any improvement in yields. However, this finding led us to believe that ketenimines might be undergoing rearrangement to afford a nitrile, and the resulting nitrile might be reacting with diyne in presence of Ni-catalyst to yield the pyridine product.[15-16]

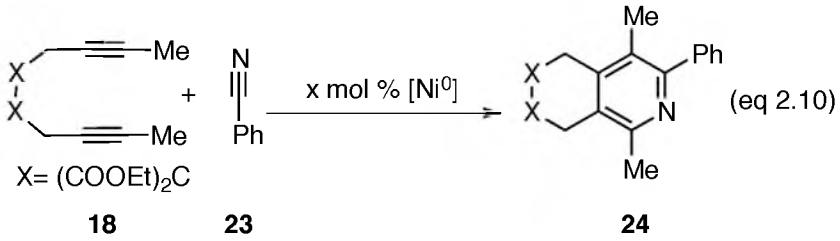


Surprised by this result, particularly in light of previous difficulties associated with pyridine formation using Ni/PR_3 catalysts (see above), we evaluated a variety of monodentate and bidentate phosphines as potential ligands in the nickel-catalyzed cycloaddition of diyne **18** and the simple, unactivated benzonitrile **23** at 100 °C (eq 2.10,

Table 2.2). As expected, in most cases, little to no pyridine product was observed despite good conversion of the diyne.[17] From the pool of monodentate phosphines evaluated (entries 1–5), only moderate catalytic activity was observed in reactions performed with PPh_3 (θ = 145°) and PCy_3 (θ = 170°). Even poorer catalytic activity was observed when the slightly larger monodentate phosphine P(o-tol)$_3$ (θ = 194°) was used.[18]







In general, bidentate phosphines did not fare any better. DPPE (β=85°) was ineffective towards pyridine formation (entry 6). Although the pyridine product was observed when bidentate ligands with larger bite angles such as BINAP (β=92°) or DPPF (β=96°) were employed (entries 7 and 8), yields were still marginal. Surprisingly, a

dramatic increase in pyridine formation occurred when Xantphos (β=111°), a bidentate ligand with a large bite angle, was evaluated (entry 9).[18] Further optimization (entries 10–12) led to a system that provided pyridine **24** in excellent yields under mild reaction conditions (3 mol % Ni-catalyst at RT for 3 h). Thus, in contrast to our previous hypothesis, sterics may play an equally or more important role than electronics in promoting both the challenging oxidative coupling and reductive elimination of C-N bond.

The reaction has a broad substrate scope and tolerates a variety of functional groups (Table 2.3). Yields obtained using the Ni/NHC catalyst system are provided in parentheses for direct comparison. Diyne **18** reacted with benzonitrile **23** to afford **24** in excellent yields (entry 1). Electron-withdrawing groups (4-CF_3, 3,5-F_2; entries 4 and 5) on the arylnitrile afforded the cycloadduct in higher yields than arylnitriles bearing electron-donating groups (2-Me, 4-OMe; entries 2 and 3). 2-Napthylnitrile (**33**) also afforded the pyridine product **34** in excellent yield (entry 6). Interestingly, diyne **35** reacted with a variety of nitriles to provide 5,6-membered fused-ring systems in higher yields than those obtained with the Ni/SIPr catalyst system (entries 7–10, 13, 14). In addition, similar trends in the yields of the pyridine products derived from diyne **35** were observed when the electronics on the arylnitrile were modified (i.e., electron-withdrawing substituents gave higher yields than substrates bearing electron-donating substituents). However, these effects were not as pronounced as they were with the original Ni/NHC system (yields in parentheses; entry 9 versus entry 10). Nitrile **41** bearing an activated olefin successfully reacted with **35** to afford **42** (entry 12) in excellent yield, although an elevated temperature was required. Notably, no product arising from incorporation of the

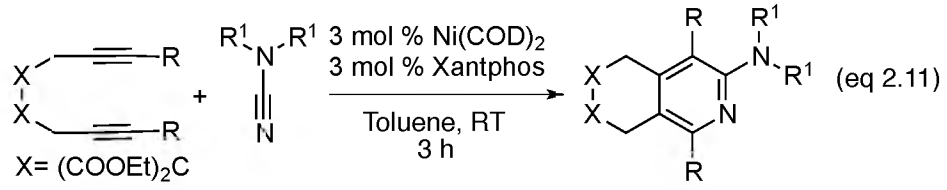
olefin was observed.[19] The challenging alkyl nitriles (**7** and **44**) also afforded the desired pyridines in excellent yields (entries 13 and 14). Similarly, sulfonamide diyne **46** and ether backbone **48** reacted with benzonitrile **23** to yield products in good yields (entries 15 and 16). The Thorpe–Ingold effect was not a necessity of this reaction as diyne **50** reacted to afford the cycloadduct **5** in excellent yield (entry 17). It is important to note that all nitriles evaluated were not purified prior to use; instead, they were used as received from commercial suppliers.

The efficacy of the Ni/Xantphos cycloaddition catalyst system was compared to other, state-of-the-art transition-metal catalysts based on Co, Ru, Rh, and Ni (Table 2.4, entries 1–5 versus 6). Specifically, diyne **18** and benzonitrile **23** were subjected to a variety of catalytic conditions and monitored for pyridine formation. Even after 24 h in the presence of a large excess of nitrile (20 equiv), full conversion of the diyne was not reached with 5 mol % [Co] catalyst (Table 2.4, entry 1). Also, the desired cycloadduct was formed in only 70 % yield.

A Rh/binap catalyst developed by Tanaka *et al.* is known for exhibiting excellent catalytic activity for activated nitriles (an approach complementary to the Ru-catalyzed cycloaddition developed independently by the groups of Yamamoto and Saà). However, replacement of binap with Segphos was required when simple nitriles, such as acetonitrile or benzonitrile, were employed. Although excellent yield and conversion were observed at 60 °C, the reaction afforded the pyridine in lower yield at room temperature with the Rh/Segphos catalyst (Table 2.4, entries 2 and 3 versus entry 6). The [Ru] catalyst was found to be completely ineffective towards pyridine product formation (entry 4). Although excellent conversion of the diyne **18** was observed with the Ni/SIPr

catalyst, **24** was produced in lower yields than with the Ni/Xantphos system (entry 5 versus entry 6). Thus, lower catalyst loading, milder reaction conditions, and equimolar substrate stoichiometry make Ni/Xantphos a more efficient catalyst for coupling of diynes and unactivated nitriles.

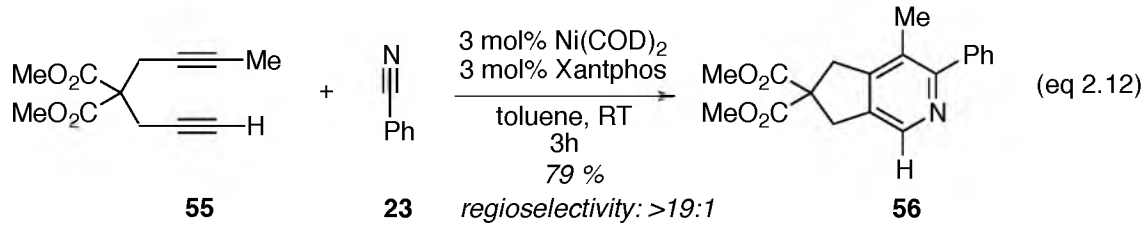
Our group recently reported that Ni/NHC catalyzes the cycloaddition of diynes and cyanamides to access 2-aminopyridines.[20] These cycloadditions possessed an expanded substrate scope as terminal diynes were successfully converted into pyridine products. However, SIPr was required as a ligand rather than the standard IMes ligand employed for the coupling of internal diynes and cyanamides. The Ni/Xantphos system was evaluated and proved effective for the coupling of particularly challenging substrates (eq 2.11, Scheme 2.3). Specifically, 2,7-diynes (i.e., **18** and tetraethyl octa-1,7-diyne-4,4,5,5-tetracarboxylate) were successfully reacted with either pyrrolidine-1-carbonitrile, morpholine-4-carbonitrile or *N*,*N*-diallylcyanamide to give 6,6-fused bicyclic products (**52**, **53**, **54**). In addition, the same Ni/Xantphos system could be used for both internal and terminal diynes. Importantly, diallyl cyanamide, a cyanamide that is unreactive with the Ni/IMes catalyst, gave **54** in good yield.

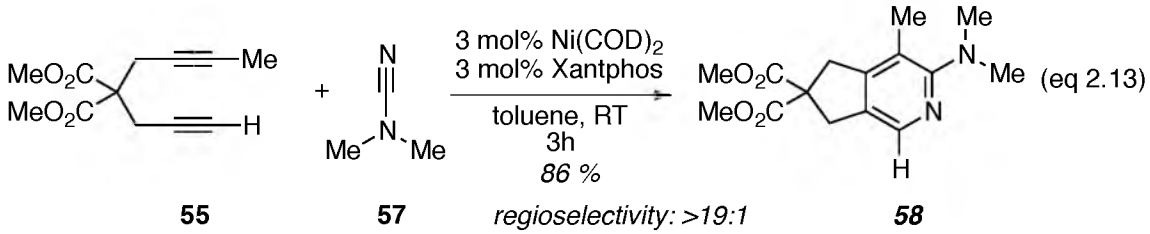


(eq 2.11)

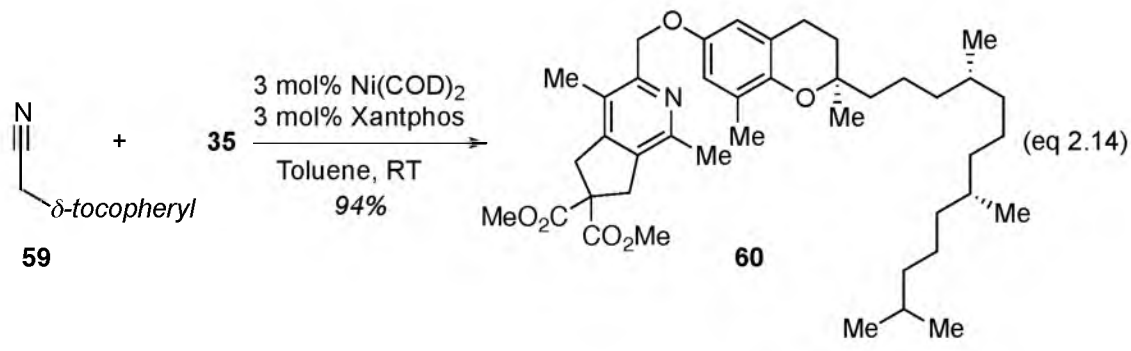
Treatment of the unsymmetrical diyne **55** with benzonitrile **23** led to the regioselective formation of the cycloadduct **56** (eq 2.12). Despite the higher reactivity of terminal diynes, the regioselectivity is governed by the insertion of a less-sterically hindered alkyne (bearing H on the terminal carbon atom) in the azametallacycle formed

by initial oxidative coupling of the internal alkyne (bearing Me on the terminal carbon atom) and **23** (see Figure 2.1). Analogous to the reaction of the diyne **55** and **23**, *N*,*N*-dimethylcyanamide **57** was also regioselectively coupled with **55** to afford the 2-aminopyridine **58** (eq 2.13).[21]





The combination of high yields, mild reaction conditions, and, importantly, efficient stoichiometry led us to investigate the use of this system to rapidly couple a diyne with a complex nitrile. Specifically, equimolar amounts of both the diyne **35** and δ-tocopherol-derived nitrile **59** were subjected to the Ni/Xantphos catalyst at room temperature. After only 3 h, pyridine **60** was obtained in 94 % yield (eq. 2.14). Thus, excess nitrile is not required to obtain high yields of potential pyridine bioconjugates.



Conclusion

In summary, we discovered a Ni/phosphine system that promotes both oxidative coupling between an alkyne and a nitrile as well as C—N bond-forming reductive elimination. The combination of catalytic amounts of Xantphos and Ni^0 produced a variety of pyridines from unactivated nitriles and diynes under mild and efficient reaction conditions. Future studies focused on understanding the mechanism of this reaction and the application of this methodology toward the synthesis of bioconjugates are ongoing. Specifically, addressing the current limitations associated with our methodlogy: (a) failure of terminal diynes to participate in the cycloaddition reaction with unactivated nitriles, and (b) failure of fully intermolecular reaction, would greatly expand the synthetic utility of this methodology.

General experimental

All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2-filled glove box unless otherwise noted. Toluene was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. THF was freshly distilled from Na/benzophenone. $Ni(COD)_2$ was purchased from Strem and used without further purification. The diynes were prepared according to literature procedure.[14] All other reagents were purchased and used without further purification unless otherwise noted.

^1H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 300 and 125 MHz, respectively, unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^1H and to the center line of a triplet at 77.23 ppm for ^{13}C. The

abbreviations s, d, dd, dt, dq, t, q, and quint stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, quartet, and quintet, in that order. All ^{13}C NMR spectra were proton decoupled. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer.

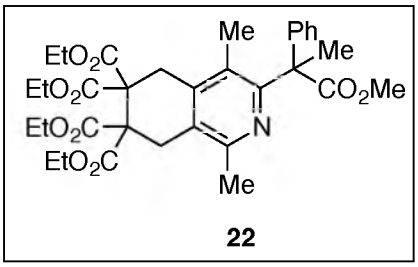
Gas Chromatography was performed on an Agilent 6890 gas chromatograph with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 °C; temperature ramp rate 50 °C/min.; final temperature: 300 °C held for 7 minutes; detector temperature: 250 °C.

Ligand screening

In a nitrogen-filled glove box, diyne **18** (10 mg, 1 equiv.) and ketenimine[22] **21** (1.2 equiv.) were added to an oven-dried screw-cap vial equipped with a magnetic stir bar. In separate vials, $Ni(COD)_2$ and ligand were weighed and dissolved in toluene. The catalyst solution (10 mol %) was added to the reaction mixtures. The vials were sealed, brought out of the glove box, and stirred @ 100 °C for 24 h. The crude reaction mixtures were analyzed by GC.

Tetraethyl 3-(1-methoxy-1-oxo-2-phenylpropan-2-yl)-1,4-dimethylisoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (**22**)

In a nitrogen-filled glove box, diyne **18** (52.1 mg, 0.12 mmol, 0.1M) and ketenimine[2] **21** (28.0 mg, 0.14 mmol) were added to an oven-dried screw-cap vial equipped with a magnetic stir bar. In a separate vial, $Ni(COD)_2$ and Xantphos were weighed (in 1:1 molar ratio) and dissolved in toluene. 10



22

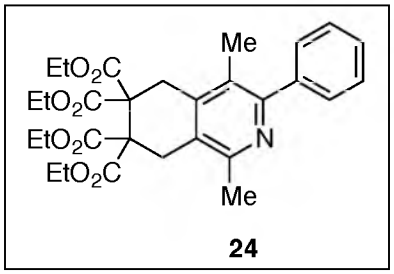
mol% Catalyst solution was added to the reaction mixture. The reaction vessel was sealed, brought out of the glove box, and stirred @ 100 °C for 24 h. The resulting reaction mixture was concentrated, and purified by flash column chromatography using first 15% EtOAc, and then 30% EtOAc in hexanes to afford the title compound **22** as pale oil, 29% yield. ^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.25 (m, 5H), 4.20 (m, 8H), 3.68 (s, 3H), 3.33 (s, 2H), 3.30 (s, 2H), 2.42 (s, 3H), 1.98 (s, 3H), 1.68 (s, 3H), 1.24 (m, 12H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 175.7, 170.1, 169.9, 157.7, 151.9, 143.0, 142.3, 128.1, 128.0, 126.5, 125.2, 62.2, 59.7, 57.5, 56.6, 52.5, 32.8, 32.1, 24.7, 22.8, 15.7, 14.0. IR (CH_2Cl_2, cm^{-1}): 2984, 2935, 1735, 1600, 1575, 1446, 1368, 1270, 1241, 1203, 1096, 1036, 864, 700. HRMS (ESI): calcd for $C_{33}H_{42}NO_{10}$ $[M+1]^+$ 612.2809, found 612.2806.

General procedure for cycloaddition of diynes and nitriles

In a nitrogen-filled glove box, diyne (1 equiv, 0.1 M) and nitrile (1.5 equiv) were added to an oven-dried screw-cap vial equipped with a magnetic stir bar. In a separate vial, $Ni(COD)_2$ and Xantphos were weighed (in 1:1 molar ratio) and dissolved in toluene. The catalyst solution (3 mol %) was added to the reaction mixture. The vial was sealed and brought out of the glove box. The reaction was stirred @ RT for 3 h. The resulting reaction mixture was concentrated and purified by flash column chromatography.

Tetraethyl 1,4-dimethyl-3-phenylisoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (**24**)

The general procedure was used with 51.3 mg (0.12 mmol, 0.1 M) of diyne **18**, 18.7 mg (0.18 mmol) of nitrile **23**, and 3 mol % of catalyst in toluene. The



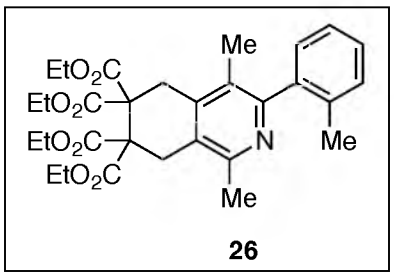
24

reaction mixture was purified via flash column chromatography using 30% to 50% ethyl acetate in hexanes to afford title compound **24** as colorless oil, 98% yield.

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.43 (m, 4H), 7.36 (m, 1H), 4.23 (m, 8H), 3.43 (s, 4H), 2.50 (s, 3H), 2.17 (s, 3H), 1.25 (m, 12H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 169.99, 169.95, 155.6, 153.0, 141.42, 141.39, 129.4, 128.2, 127.6, 125.9, 125.3, 62.2, 57.1, 56.9, 33.1, 32.2, 22.5, 15.9, 13.9. IR (CH_2Cl_2, cm^{-1}): 2984, 1736, 1568, 1447, 1368, 1271, 1240, 1203, 1095, 1053, 864, 702. HRMS (ESI): calcd for $C_{29}H_{36}NO_8$ $[M+1]^+$ 526.2441, found 526.2441.

Tetraethyl 1,4-dimethyl-3-(o-tolyl)isoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (**26**)

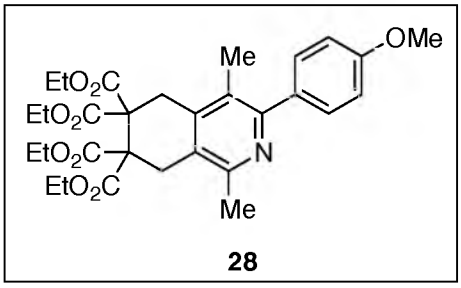
The general procedure was used with 49.0 mg (0.11 mmol, 0.1 M) of diyne **18**, 20.3 mg (0.17 mmol) of nitrile **25**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 30% to 50% ethyl acetate in hexanes to afford the title compound **26** as colorless oil, 87% yield.



26

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.32 (d, 2H, J = 8Hz), 7.23 (d, 2H, J = 8Hz), 4.23 (m, 8H), 3.43 (s, 4H), 2.49 (s, 3H), 2.39 (s, 3H), 2.17 (s, 3H), 1.25 (m, 12H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 170.0, 169.9, 155.6, 152.9, 141.2, 138.5, 137.2, 129.3, 128.9, 125.8, 62.1, 57.1, 56.9, 33.1, 32.2, 22.5, 21.4, 15.9, 13.9. IR (CH_2Cl_2, cm^{-1}):2983, 2924, 1734, 1445, 1367, 1205, 1095, 1039, 864, 734, 578. HRMS (ESI): calcd for $C_{30}H_{38}NO_8$ $[M+1]^+$ 540.2597, found 540.2591.

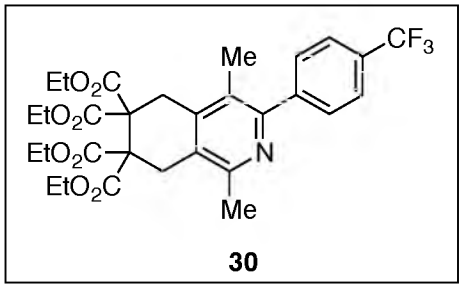
Tetraethyl 3-(4-methoxyphenyl)-1,4-dimethylisoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (**28**)



28

The general procedure was used with 48.4 mg (0.11 mmol, 0.1 M) of diyne **18**, 20.3 mg (0.17 mmol) of nitrile **27**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 30% to 50% ethyl acetate in hexanes to afford the title compound **28** as colorless oil, 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.37 (d, 2H, J = 8Hz), 6.96 (d, 2H, J = 8Hz), 4.23 (m, 8H), 3.84 (s, 3H), 3.43 (s, 4H), 2.49 (s, 3H), 2.18 (s, 3H), 1.26 (m, 12H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 170.0, 169.9, 159.2, 155.3, 152.9, 141.3, 134.0, 130.7, 125.8, 125.0, 113.7, 62.20, 62.19, 57.2, 56.9, 55.5, 33.1, 32.2, 22.5, 16.0, 13.9. IR (CH_2Cl_2, cm^{-1}):2984, 2938, 2838, 1734, 1610, 1573, 1513, 1427, 1367, 1247, 1203, 1110, 1036, 965. HRMS (ESI): calcd for $C_{30}H_{38}NO_9$ $[M+1]^+$ 556.2547, found 556.2551.

Tetraethyl 1,4-dimethyl-3-(4-(trifluoromethyl)phenyl)isoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (**30**)

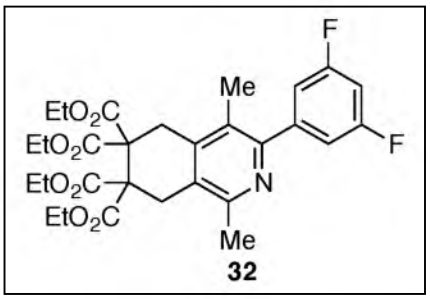


30

The general procedure was used with 53.9 mg (0.12 mmol, 0.1 M) of diyne **18**, 32.7 mg (0.19 mmol) of nitrile **29**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **30** as colorless oil, 99% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.68 (d, 2H, J = 8Hz), 7.58 (d, 2H, J = 8Hz), 4.24 (m, 8H), 3.44 (d, 4H, J = 3.2 Hz), 2.50 (s, 3H), 2.17 (s, 3H), 1.26 (m, 12H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 169.93, 169.89, 154.1, 153.4, 145.0, 141.7, 129.9, 126.1, 126.0, 125.29 (q, J = 2.85 Hz), 62.29, 62.26, 57.1, 56.8, 33.1, 32.3, 22.5, 15.8, 13.9. IR (CH_2Cl_2, cm^{-1}):2985, 2940, 1735, 1618, 1565, 1428, 1392, 1367, 1325, 1271, 1203, 1165, 1123, 1064, 966, 853. HRMS (ESI): calcd for $C_{30}H_{35}NO_8F_3$ $[M+1]^+$ 594.2315, found 594.2321.

Tetraethyl 3-(3,5-difluorophenyl)-1,4-dimethylisoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (**32**)



32

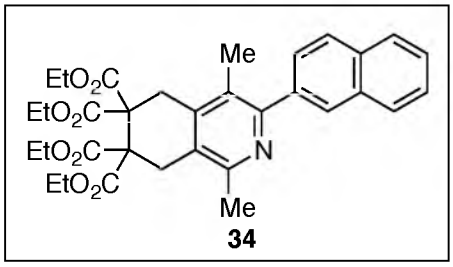
The general procedure was used with 53.4 mg (0.12 mmol, 0.1 M) of diyne **18**, 26.3 mg (0.18 mmol) of nitrile **31**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **32** as colorless oil, >99% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.97 (m, 2H), 6.80 (m, 1H), 4.23 (m, 8H), 3.42 (d, 4H, J = 4.4 Hz), 2.49 (s, 3H), 2.17 (s, 3H), 1.26 (m, 12H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 169.89, 169.86, 162.89 (dd, J = 185 Hz , 9.65 Hz), 153.4, 153.1 (t, J = 1.95 Hz), 141.8, 126.2, 112.6 (m), 103.1 (t, J = 18.75 Hz)), 57.0, 56.8, 33.1, 32.2, 22.5, 15.7, 13.9. IR (CH_2Cl_2, cm^{-1}):3084, 2985, 2939, 1733, 1624, 1594, 1428, 1368, 1269, 1203, 1116, 1053, 987, 864, 736, 699.93. HRMS (ESI): calcd for $C_{29}H_{34}NO_8F_2$ $[M+1]^+$ 562.2252, found 562.2253.

Tetraethyl 1,4-dimethyl-3-(naphthalen-2-yl)isoquinoline-6,6,7,7(5H,8H)-

tetracarboxylate (**34**)

The general procedure was used with 42.4 mg (0.10 mmol, 0.1 M) of diyne **18**, 23.0 mg (0.15 mmol) of nitrile **33**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **34** as colorless oil, 96% yield.

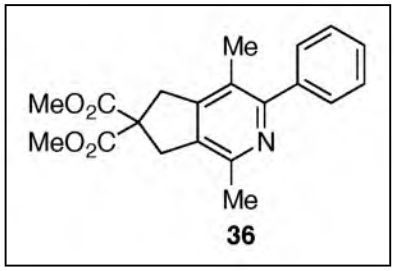


34

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.90 (m, 4H), 7.60 (m, 1H), 7.50 (m, 2H), 4.23 (m, 8H), 3.42 (d, 4H, J = 3.2 Hz), 2.55 (s, 3H), 2.20 (s, 3H), 1.26 (m, 12H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 170.0, 155.5, 153.1, 141.4, 138.8, 133.3, 132.9, 128.5, 128.4, 127.85, 127.80, 127.6, 126.1, 125.4, 62.2, 57.0, 33.1, 32.2, 22.6, 16.0, 13.9. IR (CH_2Cl_2, cm^{-1}):3056, 2984, 2938, 1733, 1565, 1429, 1367, 1270, 1203, 1095, 1052, 912, 863, 823, 732. HRMS (ESI): calcd for $C_{33}H_{38}NO_8$ $[M+1]^+$ 576.2597, found 576.2606.

Dimethyl 1,4-dimethyl-3-phenyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**36**)

The general procedure was used with 46.0 mg (0.19 mmol, 0.1 M) of diyne **35**, 30.1 mg (0.29 mmol) of nitrile **23**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **36** as solid, 92% yield. ^{1}H NMR and ^{13}CNMR was consistent with reported data.[3]

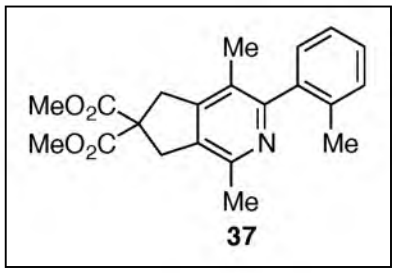


36

Dimethyl 1,4-dimethyl-3-(o-tolyl)-5H-cyclopenta[c]pyridine-

6,6(7H)-dicarboxylate (**37**)

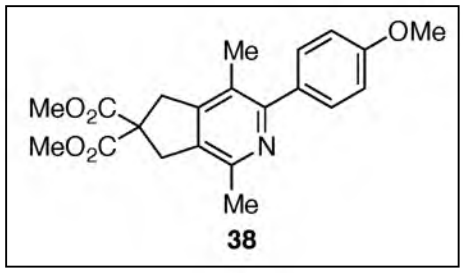
The general procedure was used with 45.6 mg (0.19 mmol, 0.1 M) of diyne **35**, 33.9 mg (0.28 mmol) of nitrile **25**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **37** as solid, 85% yield. ^{1}H NMR and ^{13}CNMR was consistent with reported data.[3]



37

Dimethyl 3-(4-methoxyphenyl)-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**38**)

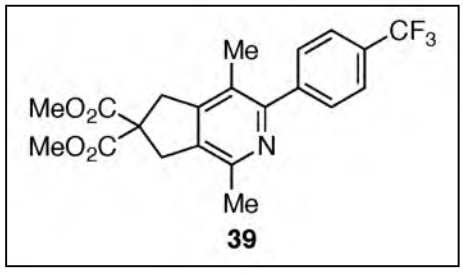
The general procedure was used with 45.3 mg (0.19 mmol, 0.1 M) of diyne **35**, 38.2 mg (0.28 mmol) of nitrile **27**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 30% to 50% ethyl acetate in hexanes to afford the title compound **38** as solid, 89% yield. ^{1}H NMR and ^{13}CNMR was consistent with reported data.[3]



38

Dimethyl 1,4-dimethyl-3-(4-(trifluoromethyl)phenyl)-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**39**)

The general procedure was used with 49.1 mg (0.20 mmol, 0.1 M) of diyne **35**, 53.3 mg (0.31 mmol) of nitrile **29**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the

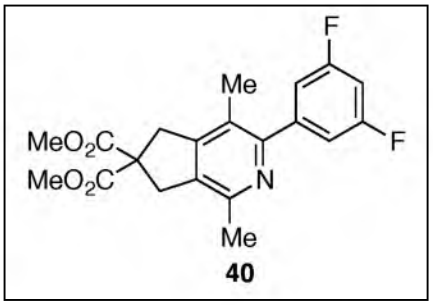


39

title compound **39** as solid, 98% yield. ^{1}H NMR and $^{13}CNMR$ was consistent with reported data. [3]

Dimethyl 3-(3,5-difluorophenyl)-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**40**)

The general procedure was used with 54.4 mg (0.23 mmol, 0.1 M) of diyne **35**, 48.0 mg (0.34 mmol) of nitrile **31**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **40** as solid, >99% yield.

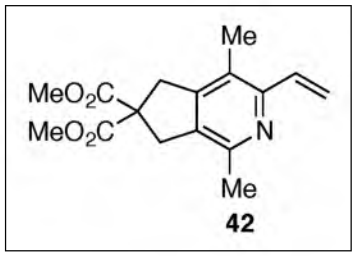


40

^{1}H NMR (300 MHz, $CDCl_3$): (ppm) 6.99 (m, 2H), 6.81 (m, 1H), 3.80 (s, 6H), 3.63 (s, 2H), 3.60 (s, 2H), 2.47 (s, 3H), 2.20 (s, 3H).^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 171.9, 163.3 (dd, J = 321 Hz , 12.3 Hz), 154.6, 151.0, 149.8, 144.0 (t, J = 8.1 Hz), 133.5, 124.4, 112.5 (m), 103.2 (t, J = 25.2 Hz), 59.5, 53.4, 40.2, 39.2, 22.0, 16.1. IR (CH_2Cl_2, cm^{-1}): 2956, 1737, 1624, 1589, 1434, 1351, 1268, 1201, 1166, 1117, 1063, 986, 866, 738. HRMS (ESI): calcd for $C_{20}H_{20}NO_4F_2$ $[M+1]^+$ 376.1360, found 376.1360.

Dimethyl 1,4-dimethyl-3-vinyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**42**)

The general procedure was used with 46.1 mg (0.19 mmol, 0.1 M) of diyne **35**, 15.5 mg (0.29 mmol) of nitrile **41**, and 3 mol % of catalyst in toluene but reaction mixture was heated and stirred @ 100 °C. The reaction mixture was



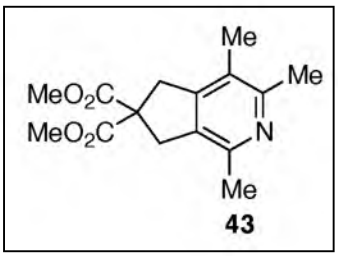
42

purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **42** as solid, >99% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.9 (dd, 1H, J = 10.5 Hz, 16.8 Hz), 6.26 (d, 1H, J = 15.6 Hz), 5.4 (d, 1H, J =10.8 Hz), 3.77 (s, 6H), 3.56 (s, 2H), 3.55 (s, 2H), 2.43 (s, 3H), 2.23 (s, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 172.0, 151.8, 150.7, 148.9, 133.2, 124.0, 118.9, 59.5, 53.3, 40.0, 39.3, 22.1, 14.6. IR (CH_2Cl_2, cm^{-1}): 2955, 1737, 1578, 1434, 1268, 1201, 1164, 1066, 929. HRMS (ESI): calcd for $C_{16}H_{20}NO_4$ $[M+1]^+$ 290.1392, found 290.1392.

Dimethyl 1,3,4-trimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**43**)

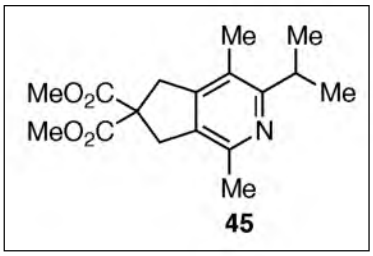
The general procedure was used with 63.4 mg (0.26 mmol, 0.1 M) of diyne **35**, 16.5 mg (0.40 mmol) of nitrile **7**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 30% to 50% ethyl acetate in hexanes to afford the title compound **43** as solid, 94% yield. ^{1}H NMR and ^{13}CNMR was consistent with reported data.[3]



43

Dimethyl 3-isopropyl-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**45**)

The general procedure was used with 61.1 mg (0.25 mmol, 0.1 M) of diyne **35**, 26.8 mg (0.38 mmol) of nitrile **44**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography

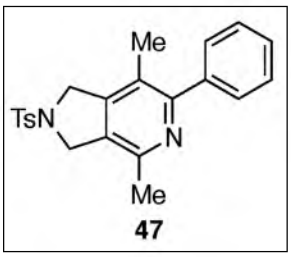


45

using 15% to 30% ethyl acetate in hexanes to afford the title compound **45** as colorless oil, 90% yield. ^{1}H NMR and ^{13}CNMR was consistent with reported data. [3]

4,7-Dimethyl-6-phenyl-2-tosyl-2,3-dihydro-1H-pyrrolo[3,4-c]pyridine (**47**)

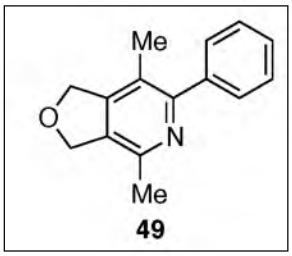
The general procedure was used with 53.4 mg (0.19 mmol, 0.1 M) of diyne **46**, 29.9 mg (0.29 mmol) of nitrile **23**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **47** as solid, 73% yield. ^{1}H NMR and ^{13}CNMR was consistent with reported data. [3]



47

4,7-Dimethyl-6-phenyl-1,3-dihydrofuro[3,4-c]pyridine (**49**)

The general procedure was used with 45.5 mg (0.37 mmol, 0.1 M) of diyne **48**, 57.6 mg (0.55 mmol) of nitrile **23**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **49** as solid, 80% yield. ^{1}H NMR and ^{13}CNMR was consistent with reported data. [3]

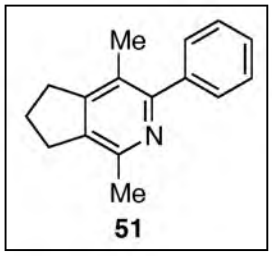


49

1,4-Dimethyl-3-phenyl-6,7-dihydro-5H-cyclopenta[c]pyridine (**51**)

The general procedure was used with 38.7 mg (0.32 mmol, 0.1 M) of diyne **50**, 49.8 mg (0.48 mmol) of nitrile **23**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% to 30% ethyl acetate in hexanes to afford the title compound **51** as solid, 93% yield.

^{1}H NMR (300 MHz,$CDCl_3$): δ (ppm) 7.45 (m, 3H), 7.36 (m, 2H),

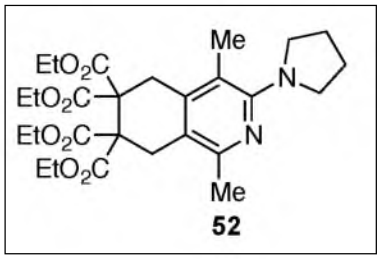


51

2.95 (t, 2H, J =7.6 Hz), 2.92 (t, 2H, J =7.6 Hz), 2.50 (s, 3H), 2.21 (s, 3H), 2.17 (q, 2H, J = 7.6 Hz). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 156.2, 153.5, 150.6, 141.4, 136.5, 129.3, 128.2, 127.5, 124.4, 32.3, 31.2, 24.4, 22.1, 16.4. IR (CH_2Cl_2, cm^{-1}): 2943 (br), 1580, 1413, 744, 700. HRMS (ESI): calcd for $C_{16}H_{18}N$ $[M+1]^+$ 224.1439, found 224.1442.

Tetraethyl 1,4-dimethyl-3-(pyrrolidin-1-yl)isoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (**52**)

The general procedure was used with 52.0 mg (0.12 mmol, 0.1 M) of diyne **18**, 14.1 mg (0.14 mmol) of N-cyano-pyrrolidine, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using first 15%, 30%, and then 50% ethyl acetate in hexanes to afford the title compound **52** as colorless oil (it starts to turn pale yellow on standing), >99% yield.

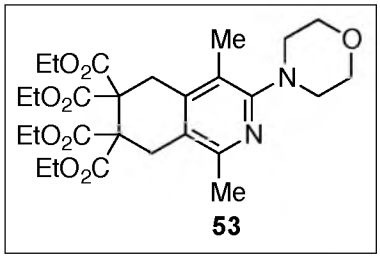


52

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.19 (m, 8H), 3.37 (m, 6H), 3.30 (s, 2H), 2.34 (s, 3H), 2.12 (s, 3H), 1.87 (q, 4H, J = 3.2 Hz), 1.23 (m, 12H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 170.2, 170.1, 158.0, 150.2, 141.6, 118.1, 115.8, 62.0, 61.9, 57.4, 57.1, 50.4, 33.1, 31.8, 25.5, 22.4, 14.8, 13.9. IR (CH_2Cl_2, cm^{-1}): 2982, 1735, 1571, 1429, 1271, 1203, 1051. HRMS (ESI): calcd for $C_{27}H_{39}N_2O_8$ $[M+1]^+$ 519.2706, found 519.2706.

Tetraethyl 3-morpholinoisoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (**53**)

The general procedure was used with 52.0 mg (0.13 mmol, 0.1 M) of diyne **18**, 22.1 mg (0.19 mmol) of N-cyano-morpholine, and 3 mol % of catalyst in toluene.



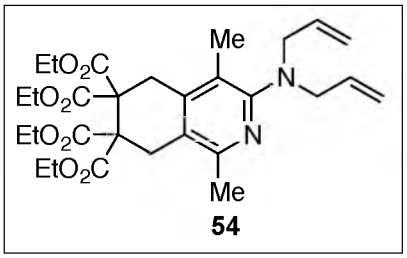
53

The reaction mixture was purified via flash column chromatography using first 15%, 30%, and then 50% ethyl acetate in hexanes to afford the title compound **53** as slightly pale yellow oil, 75% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.97 (s, 1H), 6.37 (s, 1H), 4.20 (m, 8H), 3.80 (t, 4H, *J* = 4.8 Hz), 3.43 (d, 2H, *J* = 12.4 Hz), 3.42 (d, 2H, *J* = 4.8 Hz), 1.23 (m, 12H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 169.8, 169.7, 158.7, 147.5, 143.9, 119.3, 105.5, 66.9, 62.13, 62.10, 57.7, 57.2, 46.1, 34.7, 31.5, 13.9. IR (CH_2Cl_2, cm^{-1}): 2982, 1735, 1608, 1492, 1425, 1367, 1264, 1118, 1041. HRMS (ESI): calcd for $C_{25}H_{35}N_2O_9$ $[M+1]^+$ 507.2343, found 507.2346.

Tetraethyl 3-(diallylamino)-1,4-dimethylisoquinoline-6,6,7,7(5H,8H)-tetracarboxylate (**54**)

The general procedure was used with 51.3 mg (0.12 mmol, 0.1 M) of diyne **18**, 17.8 mg (0.14 mmol) of diallyl cyanamide, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using first 15%, 30%, and then 50% ethyl acetate in hexanes to afford the title compound **54** as slightly pale yellow oil, 76% yield.



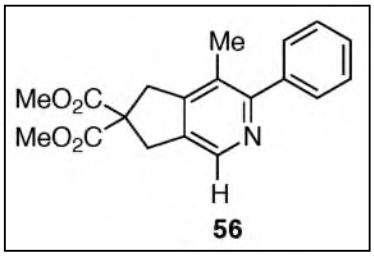
54

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 5.89 (m, 2H), 5.17 (d, 2H, *J* = 17.2 Hz), 5.07 (d, 2H, *J* = 10.2 Hz), 4.20 (m, 8H), 3.71 (d, 2H, *J* = 6Hz), 3.32 (d, 2H, *J* = 12.4 Hz), 2.35 (s, 3H), 2.14 (s, 3H), 1.22 (t, 12H, *J* = 6.8 Hz). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 170.17, 170.10, 158.6, 150.7, 142.0, 136.3, 120.6, 119.8, 116.5, 62.08, 62.04, 57.3, 57.1, 54.0, 33.2, 31.9, 22.3, 13.9. IR (CH_2Cl_2, cm^{-1}): 2983, 1736, 1570, 1443, 1367, 1443,

1367, 1269, 1205, 1095, 1038, 864. HRMS (ESI): calcd for $C_{29}H_{41}N_2O_8$ $[M+1]^+$ 545.2863, found 545.2865.

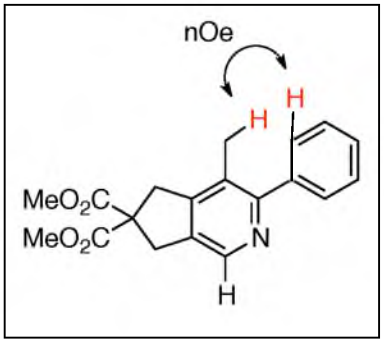
Dimethyl 4-methyl-3-phenyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**56**)

Solution of 49.0 mg (0.23 mmol, 0.1 M) of diyne **55** in toluene, was added dropwise (over a period of 1 h) to the vial containing 36.4 mg (0.35 mmol) of nitrile **23**, and 3 mol % of catalyst in toluene. Then, the reaction was stirred @ RT for another 3 h. The reaction mixture was purified via flash column chromatography using first 15%, and then 30% ethyl acetate in hexanes to afford the title compound **56** as colorless oil, 79% yield.



56

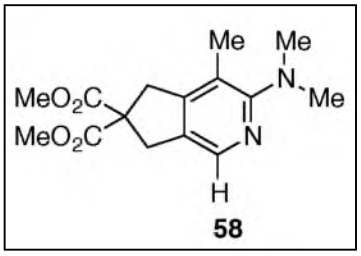
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.37 (s, 1H), 7.42 (m, 5H), 3.79 (s, 6H), 3.70 (s, 2H), 3.61 (s, 2H), 2.25 (s, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 171.8, 157.4, 149.7, 142.4, 140.5, 134.4, 129.2, 128.2, 127.8, 126.9, 59.9, 53.3, 39.9, 38.7, 16.5. IR (CH_2Cl_2, cm^{-1}): 2954, 1736, 1595, 1435, 1401, 1269, 1201, 1164, 1072, 1022, 911, 854. HRMS (ESI): calcd for $C_{19}H_{20}NO_4$ $[M+1]^+$ 326.1392, found 326.1392.



Regioselectivity was assigned on the basis of 1D-NOESY experiment on the methyl protons with aryl protons.

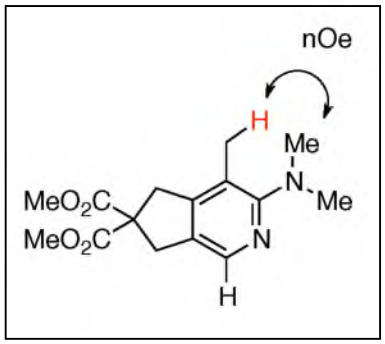
Dimethyl 3-(dimethylamino)-4-methyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**58**)

Solution of 52.0 mg (0.23 mmol, 0.1 M) of diyne **55** was added dropwise (over a period of 1 h) to the vial containing 19.6 mg (0.28 mmol) of dimethyl cyanamide, and 3 mol % of catalyst in toluene. Then, the reaction was stirred @ RT for another 3 h. The reaction mixture was purified via flash column chromatography using first 15%, 30%, and then 50% ethyl acetate in hexanes to afford the title compound **58** as oil, 86% yield.



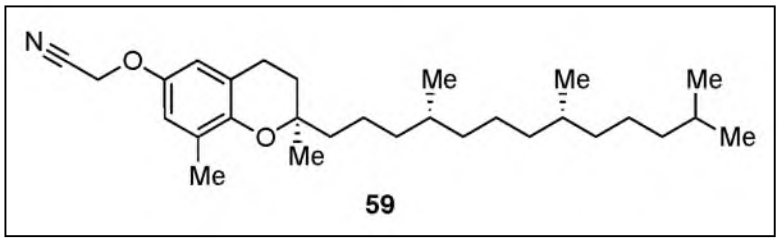
58

The regioselectivity was assigned on the basis of nOe of pyridyl methyl protons with cyanamide methyl protons. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.94 (s, 1H), 3.73 (s, 6H), 3.54 (s, 2H), 3.46 (s, 2H), 2.76 (s, 6H), 2.17 (s, 3H). ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 171.9, 161.8, 150.6, 139.7, 129.4, 120.1, 60.3, 53.2, 42.4, 39.7, 38.2, 15.1. IR (CH_2Cl_2, cm^{-1}): 2953, 1737, 1606, 1483, 1438, 1396, 1273, 1242, 1199, 1164, 1061. HRMS (ESI): calcd for $C_{15}H_{21}N_2O_4$ $[M+1]^+$ 293.1501, found 293.1501.



2-(((R)-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)acetonitrile (**59**)

To a suspension of prewashed and dried NaH (15.9 mg) in THF (4 mL), *delta*-tocopherol (177.7 mg, technical grade, about 90% purity) in THF (3 mL) was added dropwise @ 0 °C. The resulting pale yellow solution was stirred for 15 min, and then bromoacetonitrile (0.5

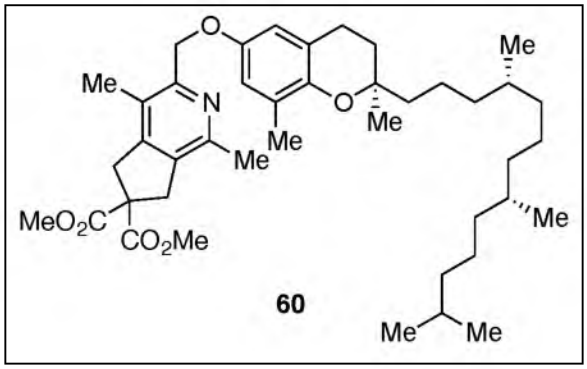


59

mL) was added and stirred overnight @ RT. The reaction mixture was purified via flash column chromatography using 10% ethyl acetate in hexanes to afford the title compound **59** as an oily compound, 146.7 mg.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.65 (d, 1H, J = 3 Hz), 6.55 (d, 1H, J = 3 Hz), 4.68 (s, 2H), 2.73 (t, 2H, J = 6 Hz), 2.16 (s, 3H), 1.77-0.86 (m, 36H) . ^{13}C NMR (75 MHz , $CDCl_3$): δ (ppm) 149.3, 148.2, 127.9, 121.4, 116.5, 115.8, 113.1, 76.1, 55.1, 40.2, 39.5, 37.6, 37.5, 37.4, 32.9, 32.8, 31.2, 28.1, 24.9, 24.6, 24.2, 22.9, 22.82, 22.80, 21.1, 19.9, 19.8, 16.4. IR (CH_2Cl_2, cm^{-1}): 2927, 2864, 1742, 1607, 1478, 1377, 1223, 1152, 1068, 857. HRMS (ESI): calcd for $C_{29}H_{47}NO_2$ $[M+K]^+$ 480.3244, found 480.3252.

Dimethyl 3-((((R)-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)methyl)-1,4-dimethyl-5H-cyclopenta[c]pyridine-6,6(7H)-dicarboxylate (**60**)

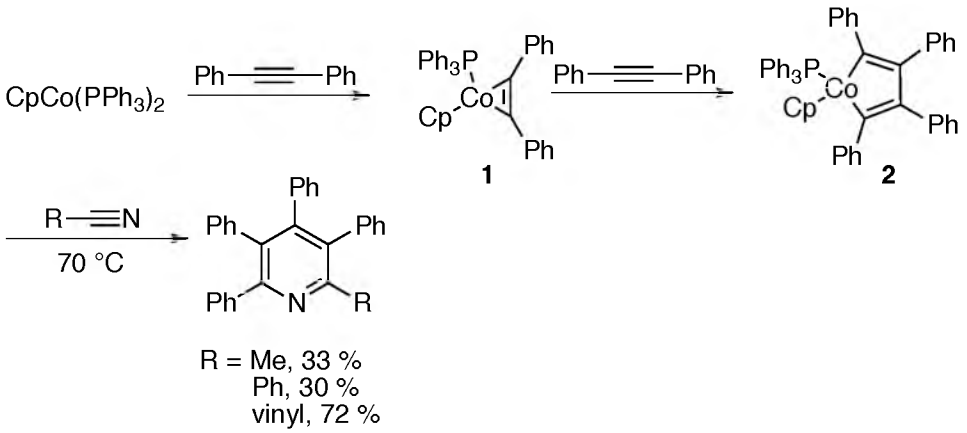


60

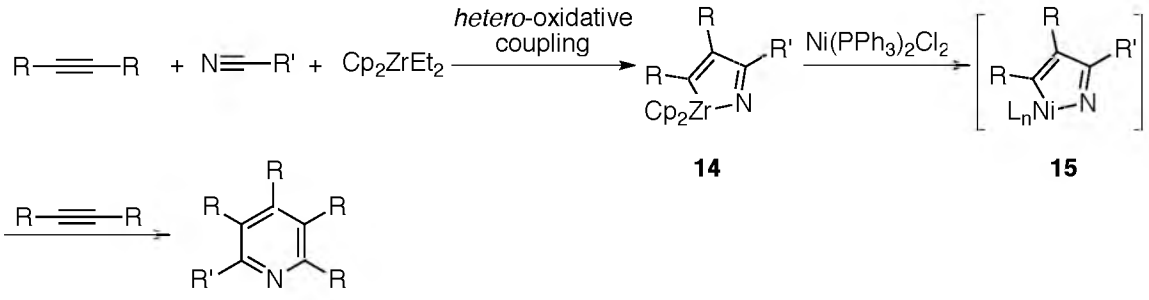
The general procedure was used with 26.0 mg (0.11 mmol, 0.1 M) of diyne **35**, 48.7 mg (0.11 mmol) of nitrile **59**, and 3 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using first 15% and then 30% ethyl acetate in hexanes to afford the title compound **60** as colorless oil, 94% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 6.67 (d, 1H, J = 3.2 Hz), 6.57 (d, 1H, J = 3.2 Hz), 5.05 (s, 2H), 3.78 (s, 6H), 3.58 (s, 2H), 3.57 (s, 2H), 2.71 (t, 2H, J = 9.6 Hz), 2.45 (s, 3H), 2.29 (s, 3H), 2.14 (s, 3H), 1.74-0.87 (m, 36H). ^{13}C NMR (75 MHz , $CDCl_3$): δ

(ppm) 171.9, 152.8, 151.5, 150.2, 149.5, 146.5, 133.9, 127.2, 127.1, 121.0, 115.8, 112.3, 75.7, 71.4, 59.6, 53.3, 40.3, 39.9, 39.5, 39.3, 37.68, 37.65, 37.64, 37.4, 33.0, 32.9, 31.5, 28.1, 25.0, 24.6, 24.3, 22.9, 22.8, 21.8, 21.2, 19.9, 19.8, 16.4, 14.6. IR (CH_2Cl_2, cm^{-1}): 2927, 1739, 1479, 1273, 1155, 1055. HRMS (ESI): calcd for $C_{42}H_{64}NO_6$ $[M+1]^+$ 678.4734, found 678.4750.



Scheme 2.1 Co-mediated cycloaddition of alkynes and nitrile



Scheme 2.2 Stoichiometric Zr- and Ni-mediated cycloaddition of alkynes and nitriles

Table 2.1 Ni-catalyzed cycloaddition of diynes and ketenimine[a]

Entry	Ligand (L_n)	Ni:L_n	Conversion[a]	Yield[a]
1	PPh_3	1:2	>99 %	-
2	P(*o*-tol)$_3$	1:2	>99 %	-
3	PCy_3	1:2	67 %	-
4	DPPB	1:1	>99 %	-
5	Ph-Xantphos	1:1	92 %	33 %
6	*t*-Bu-Xantphos	1:1	97 %	-
7	P(O-*i*-Pr)$_3$	1:3	95 %	22 %

[a] Analyzed by GC using naphthalene as an internal standard.

Table 2.2 Ni-catalyzed cycloaddition of diyne and nitrile[a]

Entry	Ligand (L_n)	Ni:L_n	**1** % Conv.[b]	**1a** % Yield[b]
1	PCy_3	1:2	>99	27
2	PBu_3	1:2	>99	-
3	PPh_3	1:2	>99	23
4	P(*o*-tol)$_3$	1:2	>99	11
5	P(O-*i*-Pr)$_3$	1:2	>99	-
6	DPPE	1:1	>99	-
7	DPPF	1:1	>99	21
8	*rac*-BINAP	1:1	>99	7
9	Xantphos	1:1	>99	>99 (86)[c]
10	Xantphos	1:1	>99	>99[d]
11	Xantphos	1:1	>99	>99[e]
12	Xantphos	1:1	>99	**>99 (98%)**[c,f]

[a] Reaction conditions: diyne (1 equiv, 0.1 M), nitrile (1.5 equiv), 10 mol % $Ni(COD)_2$, L_n (20 mol % for entries 1-5 and 10 mol % for entries 6-12), toluene, 100 °C, 24 h. [b] Analyzed by GC using naphthalene as an internal standard. [c]Isolated yields in parentheses.[d] 5 mol % catalyst. [e] 3 mol % catalyst. [f] 3 mol % catalyst, RT.

Table 2.3 Ni-catalyzed cycloaddition of diynes and nitriles[a,b]

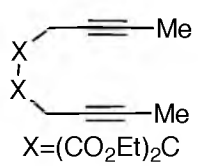
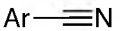
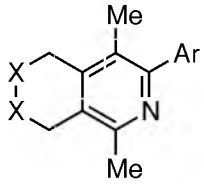
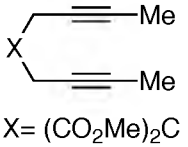
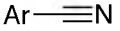
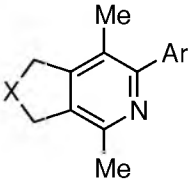
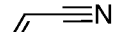
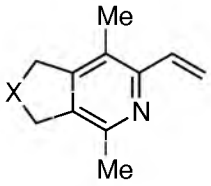
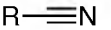
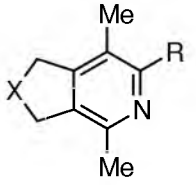
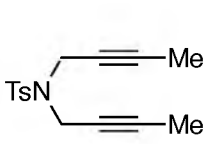
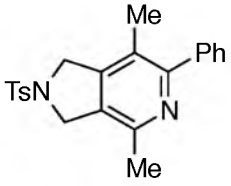
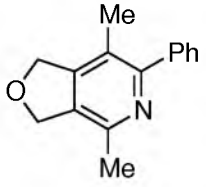
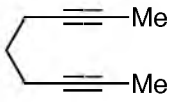
Entry	Diyne	Nitrile	Product	Yield[c]
	 X=$(CO_2Et)_2C$			
1	**18**	**23** (Ar= Ph)	**24**	98%
2	**18**	**25** (Ar= 2-Me-Ph)	**26**	87%
3	**18**	**27** (Ar= 4-OMe-Ph)	**28**	90%
4	**18**	**29** (Ar= 4-CF_3-Ph)	**30**	99%
5	**18**	**31** (Ar= 3,5-F_2-Ph)	**32**	>99%
6	**18**	**33** (Ar= 2-naphthyl)	**34**	96%
	 X= $(CO_2Me)_2C$			
7	**35**	**23** (Ar= Ph)	**36**	92 (86)[d]
8	**35**	**25** (Ar= 2-Me-Ph)	**37**	85 (81)[d]
9	**35**	**27** (Ar= 4-OMe-Ph)	**38**	89 (64)[d]
10	**35**	**29** (Ar= 4-CF_3-Ph)	**39**	98 (94)[d]
11	**35**	**31** (Ar= 3,5-F_2-Ph)	**40**	>99[d]
				
12	**35**	**41**	**42**	>99[e]
				
13	**35**	**7** (R= Me)	**43**	94 (69)[d]
14	**35**	**44** (R= *i*-Pr)	**45**	90 (72)[d]

Table 2.3 Continued

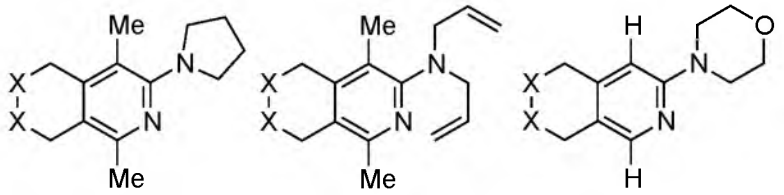
15	 **46**	**23**	 **47**	73 (78)[d]
16	 **48**	**23**	 **49**	80 (93)[d]
17	 **50**	**23**	**51**	93

[a]Reaction conditions: 3 mol % $Ni(COD)_2$, 3 mol % Xantphos, diyne (1 equiv, 0.1 M), nitrile (1.5 equiv), toluene, 100 °C, 24 h. [b]Nitriles were neither distilled nor degassed. Nitriles were used as received. [c]Yields of isolated products. [d]Yields reported for the Ni/NHC catalyst. [e]The reaction was run at 100 °C.

Table 2.4 Comparison of various state-of-the-art catalysts

Entry	Reaction Conditions	Conv. (%)[a]	Yield (%)[a]
1	5 mol % $CoCl_2 \cdot 6H_2O$, 6 mol % DPPE, excess Zn, 20 equiv nitrile, NMP, RT	86	70
2	3 mol % $[Rh(COD)_2]BF_4$, 3 mol % Segphos, 1.5 equiv nitrile, 1,2-DCE, 60 °C	>99	>99
3	3 mol % $[Rh(COD)_2]BF_4$, 3 mol % Segphos, 1.5 equiv nitrile, 1,2-DCE, RT	32	15
4	10 mol % [Cp*Ru(cod)Cl], 1.5 equiv nitrile,1,2-DCE, 60 °C	6[b]	-
5	3 mol % $Ni(COD)_2$, 3 mol % SIPr, 1.5 equiv nitrile, THF, RT	>99	80
6	3 mol % $Ni(COD)_2$, 3 mol % Xantphos, 1.5 equiv nitrile, toluene, RT	>99%	>99% (98%)[c]

[a]Analyzed by GC using naphthalene as an internal standard. [b]Analyzed by ^{1}H-NMR spectroscopy. [c]Isolated yields



Scheme 2.3 Ni-catalyzed cycloaddition of diynes and cyanamides

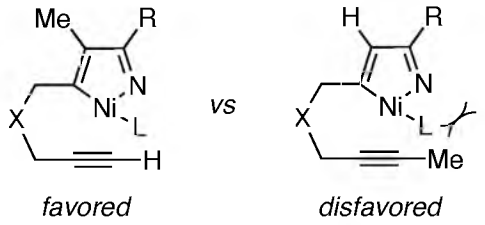


Figure 2.1 Proposed nickelacycles

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(16) The nitrile which would have been formed by rearrangement of ketinimine, was prepared from known protocols. On subjecting this nitrile with diyne in presence of a Ni-Xantphos catalyst, no pyridine product was observed. Additionally, our efforts to convert the ketinimine to nitrile under thermal conditions or in presence of Ni-Xantphos met with failure. This piece of data suggests that Ni-catalyst might be coupling the diyne and imine portion of ketinimine, and the rearrangement may be taking place at a later stage.

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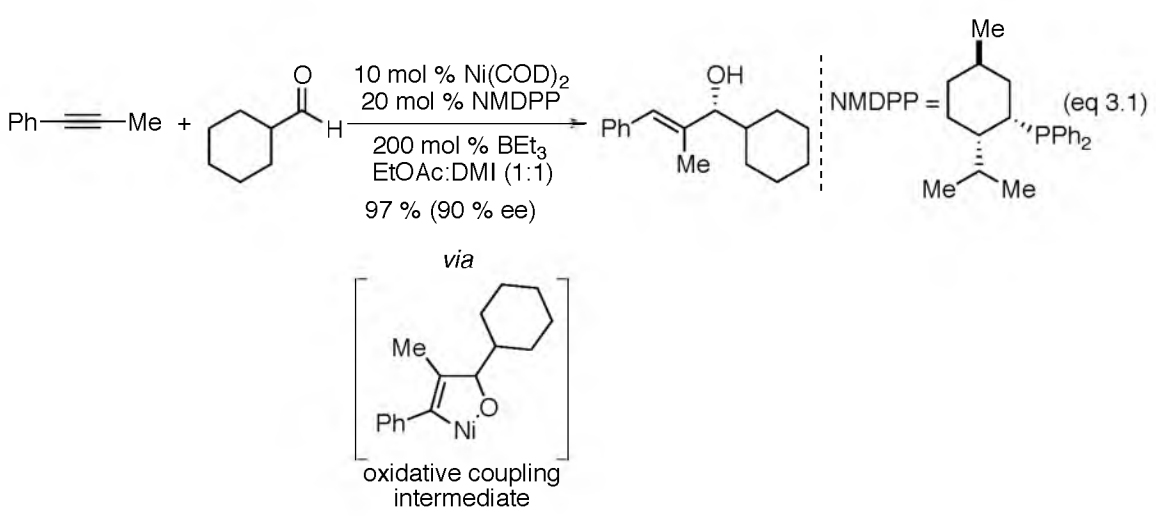
CHAPTER 3

A SINGLE-STEP APPROACH TO 3-PIPERIDONES VIA NICKEL-CATALYZED β-CARBON ELIMINATION

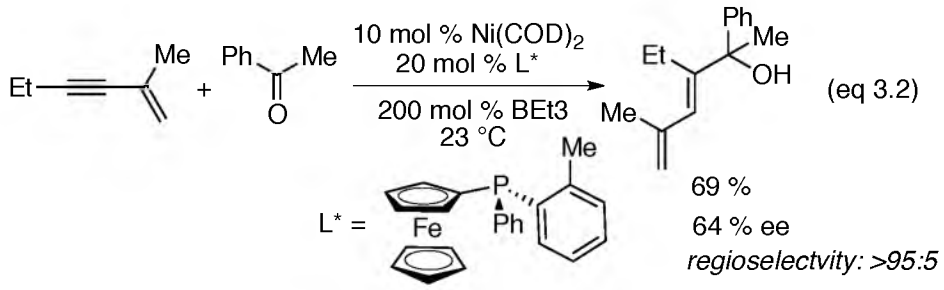
Introduction

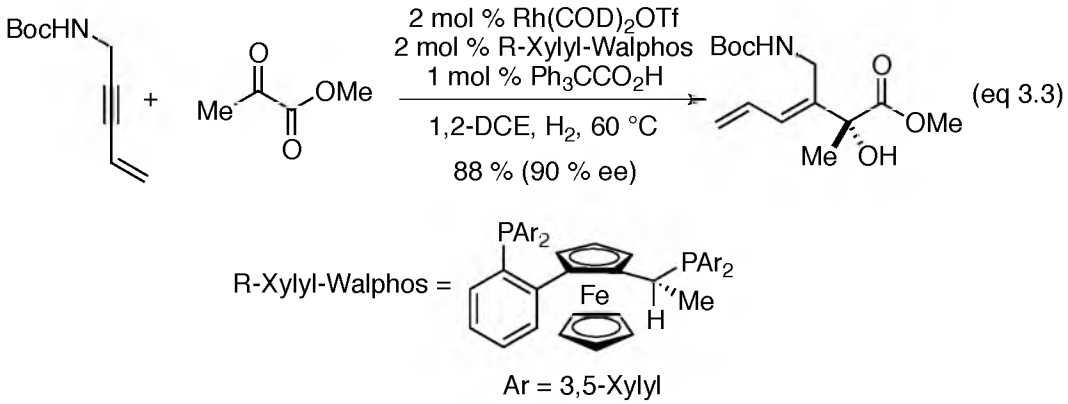
The ubiquity of piperidines in pharmaceuticals and natural products makes them attractive targets for organic synthesis.[1] Over the past few years, tremendous progress has been made in accessing highly substituted piperidines.[2] Most common methods to access piperidines rely on the derivatization of 2-piperidones and 4-piperidones. Notably, the utilization of 3-piperidones in this regard remains under utilized, which may be attributed to the lack of efficient methods to access 3-piperidones. Specifically, the aza-Achmatowicz rearrangement[3] and ring-closing metathesis[4] provide access to these motifs in an efficient fashion (Scheme 3.1). However, synthesizing highly substituted 3-piperidones is still a challenging problem. Also, most of the existing strategies rely on multistep routes, which urges the need for an operationally simple, expeditious, and efficient methodology to access these heterocycles. Recently, our group and others have reported a Ni-catalyzed coupling of carbonyl compounds with alkynes and alkenes. The Ni-catalysts promote the oxidative coupling of alkynes and aldehydes to afford a nickelacycle, which, on reaction with a suitable reductant, affords allylic alcohol (eq 3.1).[5]

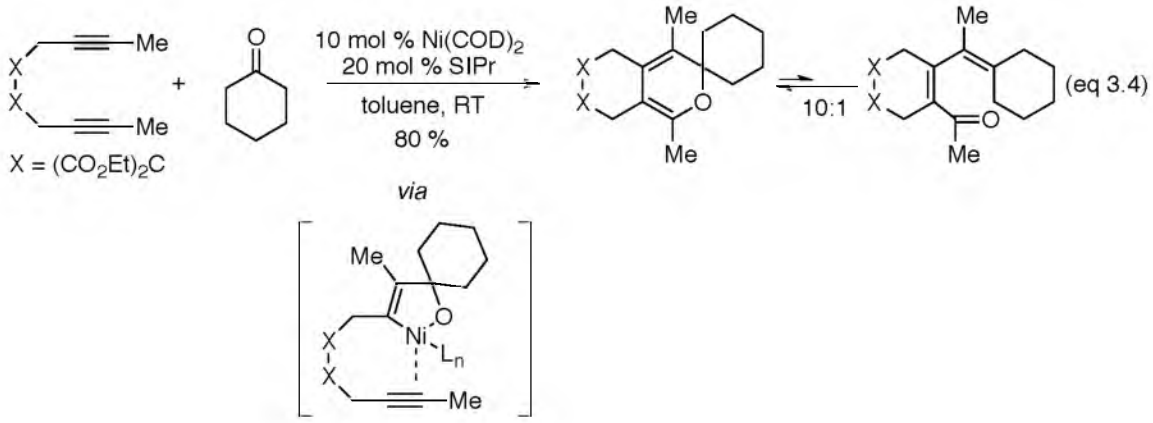
More recently, the concept of reductive coupling was extended to ketones, which are electronically as well as sterically more challenging partners in catalysis than aldehydes (eq 3.2).[6] The success of the reaction was only moderate and products were formed in high regioselectivity but only moderate enantioselectivity. The reported reaction conditions were only amenable to the coupling of activated alkynes such as 1,3-enynes and aryl-alkyl ketones. Similarly, Krische has shown that with the use of a Rh-catalyst, more activated electron-deficient ketones can also be coupled with alkynes using H_2 as a reductant (eq 3.3).[7] The reaction affords dienyl alcohols in high yields and high enantioselectivity. Notably, this reductive coupling is also limited to conjugated alkynes (1,3-enyne). These reports clearly highlight the difficulty associated with the oxidative coupling of unactivated alkynes and unactivated ketones. To address these critical issues, Louie introduced a highly active Ni-NHC catalyst, which enabled the oxidative coupling of challenging alkynes and ketones.[8] The Ni/SIPr catalyst coupled the diyne and cyclohexanone to afford a spirocyclic pyran in high yields (eq 3.4). The pyran exists in equilibrium with the ring-opened dienone form. Encouraged by these findings, the authors next subjected the enyne and ketone to a Ni/IPr catalyst. for the first time



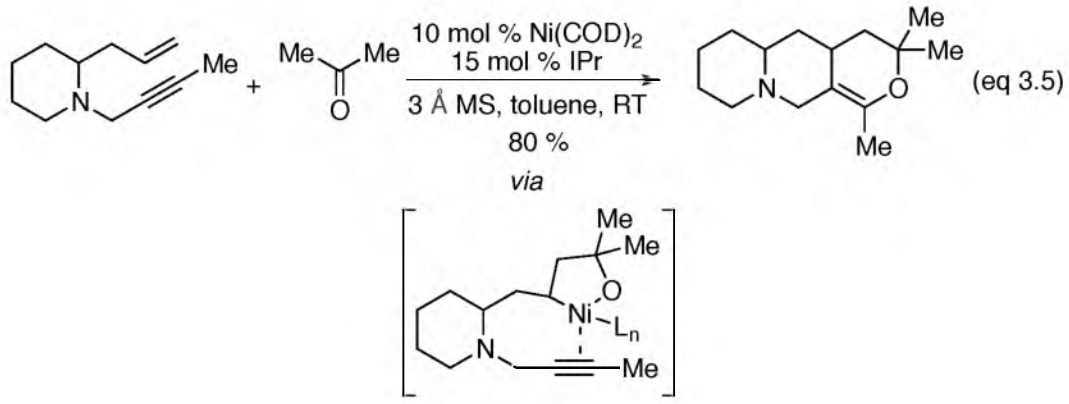
Surprisingly, the catalyst promoted the preferential oxidative coupling of an alkene over an alkyne and a ketone (eq 3.5).[8]

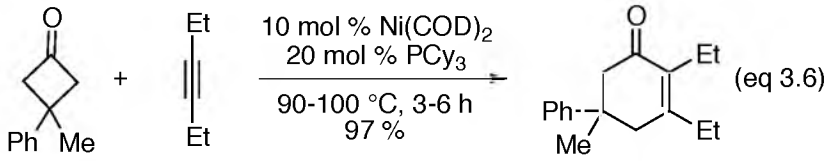


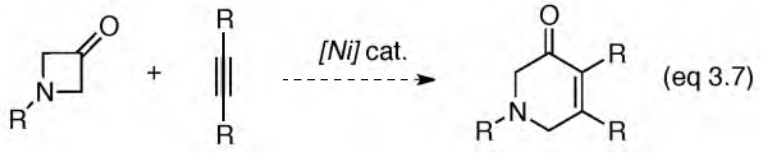




Murakami and coworkers discovered that transition metal catalysts could also be utilized to exploit the ketone moiety of cyclobutanone that can render β-carbon elimination in reactive oxidative coupling intermediates.[9] Recently, Murakami reported that cyclobutanone could be elegantly coupled with alkynes to afford highly substituted cyclohexenones (eq 3.6).[10] We surmised the coupling of 3-aza-cyclobutanones with alkynes could provide piperidines in a single step (eq 3.7).

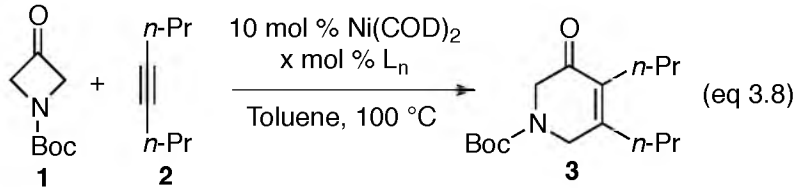






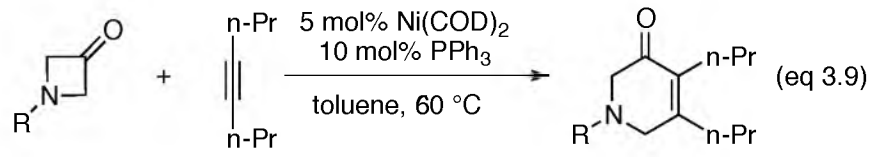
Results and discussion

For reaction optimization, we chose commercially available 1-Boc-3-azetidinone **1** and 3-octyne **2** as model substrates. Gratifyingly, a combination of $Ni(COD)_2$ and a variety of monodentate as well as bidentate ligands effected the desired cycloaddition (eq 3.8, Table 3.1). However, PPh_3 proved to be the optimal ligand in this case.[11] A report recently appeared with a similar finding that the combination of Ni(0) and PPh_3 catalyzes the coupling of azetidinones and alkynes.[12] However, in contrast to their findings, we found that the cycloaddition of alkyne and 3-azetidinones proceeds with lower catalyst loading (5 mol % rather than 10–20 mol %), lower ligand loading (10 mol % rather than 30–80 mol %), at lower temperatures (60–100 °C rather than 90–110 °C), and in shorter times (6 h rather than 17 h).[12]



(eq 3.8)

Several azetidinones bearing different N-protecting groups were prepared and investigated. The *tert*-butoxycarbonyl- and tosyl-azetidinones could be converted to piperidone products (**3** and **4**) in excellent yields (eq 3.9, Figure 3.1). However, the use of a benzhydryl protecting group did not lead to the desired cycloadduct under our optimized reaction conditions.[13] Notably, the reaction of 3-octyne and N-tosyl-azetidinone proceeded smoothly under our optimized conditions. Higher catalyst/ligand loading, higher temperature (110 °C), and prolonged reaction times were not necessary.



The substrate scope of this reaction was then investigated using 1-Boc-3-azetidinone with a variety of alkynes (Figure 3.2). The reaction with 3-octyne afforded the piperidine (**3**) in excellent yields. We also investigated the cycloaddition with a volatile alkyne, i.e., 2-butyne, which resulted in the desired product (**5**) in 95% yield. To test the effect of sterics on cycloaddition, *tert*-butyl-methyl and trimethylsilyl-methyl alkynes were investigated. Both substrates underwent cycloaddition smoothly under optimized reaction conditions, and afforded an exclusive regioisomer of 3-piperidone. The regiochemistry of piperidone in both cases was assigned on the basis of ^{1}HNMR. Interestingly, in **6**, the methyl group next to ketone shows long-range coupling with the methylene next to the olefin, and it appears as a triplet in ^{1}HNMR. In contrast, the piperidone **9** exhibited different regioselectivity pattern as the methyl group next to ketone appears as singlet. Additionally, the *tert*-butyl-methyl alkyne on reaction with tosyl azetidinone afforded a solid piperidone product **7**. The structure of **7** was unambiguously determined by single crystal X-ray crystallography (Figure 3.3). Hence, the prediction based on ^{1}HNMR was found to be consistent with the obtained crystallographic data.

The regioselective outcome of the reaction may be explained on the basis of the mechanism shown in Scheme 3.3. Initially, oxidative coupling between the alkyne and the carbonyl of the azetidinone occurs. Two intermediates, **A** or **B**, are possible. However, metallacycle **A** is favored over metallacycle **B** since the regioselectivity of **A** positions the R_L away from the quaternary center. Intermediate **A** undergoes β-carbon

elimination to form a seven-membered nickelacycle, which undergoes subsequent reductive elimination to afford the piperidine product.

Terminal alkynes are one of the most challenging substrates because of their rapid oligomerization. After a brief screening, we successfully incorporated terminal alkynes in our cycloaddition. That is, *tert*-butyl acetylene couples with azetidinone regioselectively (**8**). Interestingly, these results are in contrast to the reactivity of cyclobutanones, which fail to react with terminal alkynes as well as sterically hindered alkynes.[10] Stannyl piperidine (**10**) can also be obtained regioselectively in excellent yields when tributylstannyl-methyl alkyne was employed as a substrate. The use of 1,3-enyne led to selective formation of vinyl-piperidine (**11**) with good regioselectivity. The reaction is not limited to alkyl substituted alkynes, as diphenyl acetylene can also be successfully coupled with azetidinone to afford the piperidine (**12**).[12,14] However, these alkynes were less reactive than alkyl–alkyl alkynes, and higher temperature (100 °C) was necessary to effect the desired cycloaddition.[15]

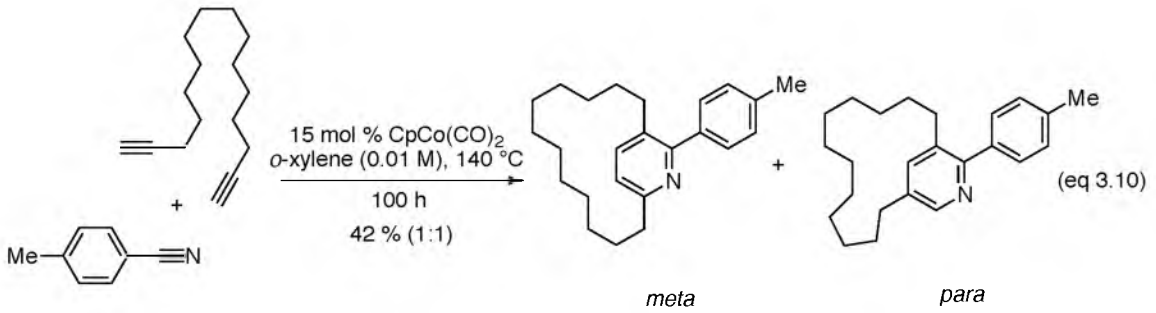
The mixed alkynes (i.e., aryl–alkyl alkynes) also react to yield the piperidine (**13**–**15**) in a regioselective fashion. Retention of regioselectivity was observed even when the electronics on the aryl ring of aryl–alkyl alkynes were perturbed (**14**, **15**). The extremely challenging aryl–silyl alkynes afforded the product (**16**) in very good yields and excellent regioselectivity, for the desired cycloadduct was observed. Furanyl (**17**) as well as thiophenyl (**18**) piperidine skeleton can also be easily accessed. Interestingly, when stannyl-phenyl alkyne is employed, the product (**19**) is obtained where the stannyl group is on the α-carbon. Thus, the aryl group, instead of the large stannyl group, seems to have a stronger affect on the regioselectivity. We believe that origin of regioselectivity lies in

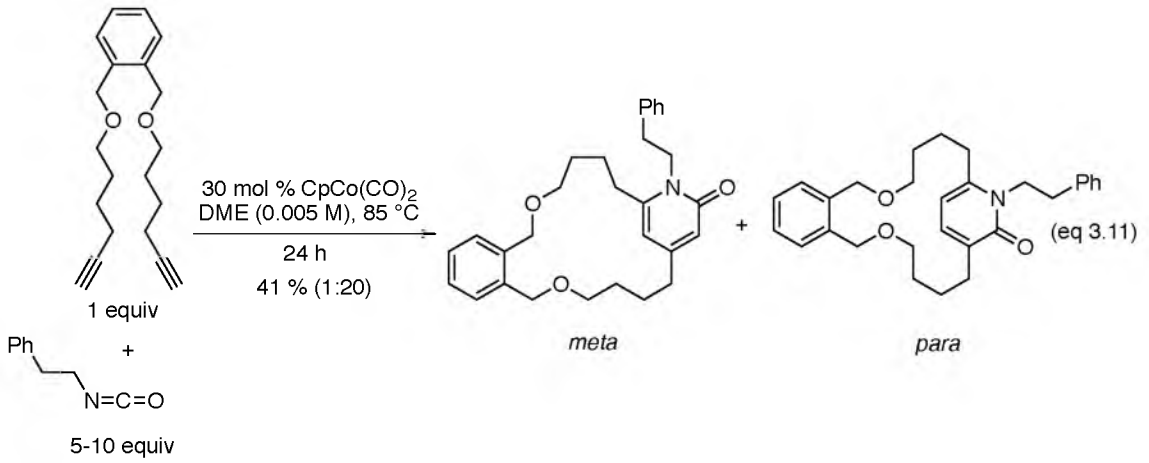
the preseferntial oxidative coupling, which is dictated by electronics of the substituents on alkynes. In other words, the oxidative coupling of electronically perturbed alkyne will favor the formation of oxidative coupling intermediate, **C** vs **D**, as shown in Scheme 3.4.

Several synthetic and medicinal chemists have shown great interest in macrocyclic heterocycles.[16] Specifically, Maryanoff and coworkers became interested in investigating the conformationally flexible macrocyclic analogs of naturally occurring staurosporine (Figure 3.4).[17] To access these pyridinocyclophanes, authors utilized a Co-mediated macrocyclization, which enabled the coupling of alkynes with nitriles (eq 3.10) as well as isocyanates (eq 3.11).[16] Unfortunately, the reaction requires high catalyst loading, high temperature, long reaction times, and slow addition of one of the reactants. The success of the reaction is only moderate with varied regioselectivity (meta *vs* para). Moreover, the macrocyclization using stoichiometric amount of cobalt-complex proceeds in extremely poor yields when the desired bis-indole diyne was subjected to [2+2+2] cycloaddition with dimethyl cyanamide (eq 3.12). The pyridinocyclophane prepared via cycloaddition strategy shows nM activity and high selectivity towards protein kinase C isozymes. To develop rapid and efficient ways to access the analogous macrocyclic heterocycles, we utilized a template-directed approach, wherein the cyclododecyne was subjected to standard reaction conditions to provide a macrocyclic piperidone (eq 3.13). We hope to exploit this idea in the near future to design and develop analogs for the protein kinase C isozymes (Scheme 3.5).

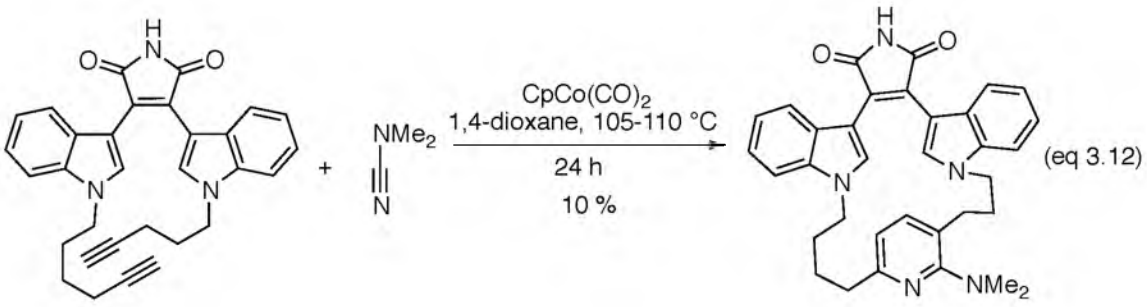
To gain insight into the migratory aptitude of a 2-substituted azetidinone, we prepared 2-benzyl-3-Boc-azetidinone (**21**) from Boc-protected phenylalanine amino acid.

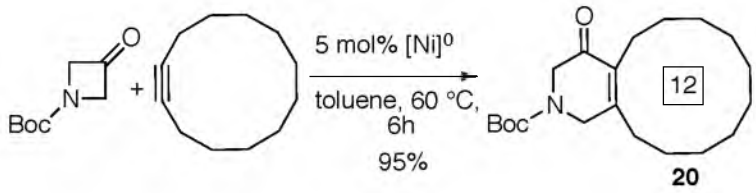
When we subjected substituted azetidinone **21** to our standard reaction conditions, regioselective formation of the piperidine product (**22**) with complete retention of enantioselecitivity (>99% ee) was obtained (eq 3.14). This observation reveals the preference for the migration of less substituted β-carbon of azetidinone on the metal (Ni) center.

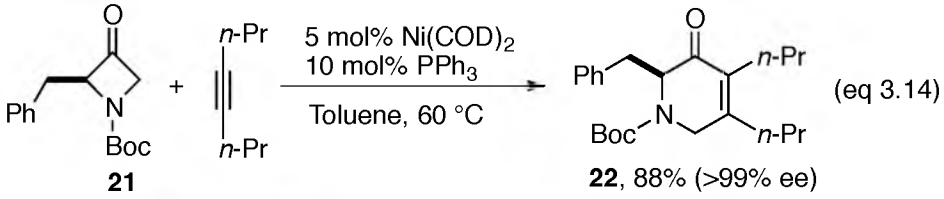


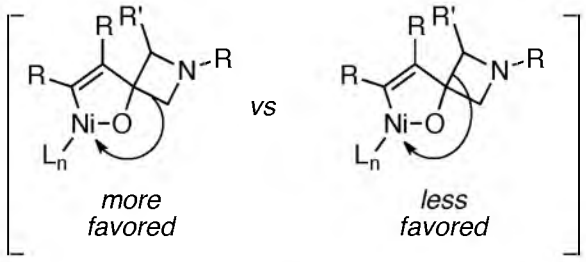


Further functionalization of the piperidine skeleton is also possible. The carbonyl moiety can be selectively reduced to the alcohol (**23**) using $NaBH_4/CeCl_3$ (eq 3.15). No loss of yield was observed for this two-step one-pot protocol. Similarly, the ketone and carbamate can be reduced using LAH and the hydroxylated *N*-methyl piperidine (**24**) can be accessed in good yields (eq 3.16).

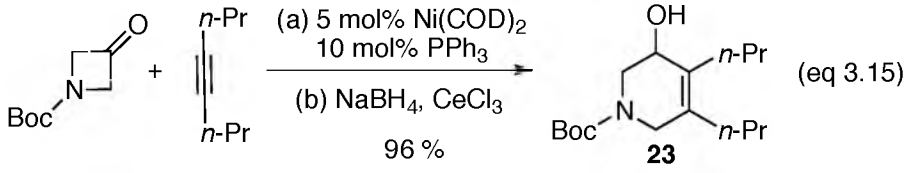

CpCo(CO)2
1,4-dioxane, 105-110 °C
24 h
10 %
NMe2
(eq 3.12)

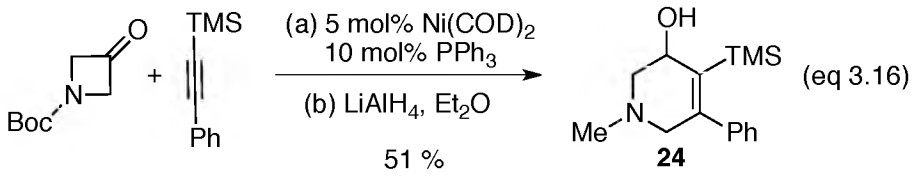

5 mol% [Ni]0
toluene, 60 °C,
6h
95%
Boc
12
20
(eq 3.13)


Ph
Boc
21
n-Pr
5 mol% Ni(COD)2
10 mol% PPh3
Toluene, 60 °C
22, 88% (>99% ee)
(eq 3.14)


Ni–O
Ln
more
favored
vs
less
favored

via


n-Pr
(a) 5 mol% Ni(COD)2
10 mol% PPh3
(b) NaBH4, CeCl3
96 %
OH
Boc
23
(eq 3.15)



(eq 3.16)

Conclusion

In conclusion, we have developed a Ni-catalyzed method for the [4 + 2]-cycloaddition reaction of azetidinones and alkynes. This reaction mechanism includes an interesting C-C bond cleavage that ultimately affords 3-piperidone products. Reaction conditions are both mild and practical and afford the *N*-heterocycles in excellent yields. We are currently applying this methodology to access a wide variety of naturally occurring indolizidine and quinazolidine alkaloids.

General experimental

All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2-filled glove box unless otherwise noted. Toluene was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. $Ni(COD)_2$ was purchased from Strem and used without further purification. 3-Boc-azetidinone was purchased from Sigma-Aldrich and used as received. All other reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. ^1H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 400 and 100 MHz, respectively, unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^1H and to the central line of a triplet at 77.23 ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, t, q, and quint stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, quartet, and quintet, in that order. All ^{13}C

NMR spectra were proton decoupled. Gas Chromatography was performed using the following conditions: initial oven temperature: 100 ºC; temperature ramp rate 50 ºC/min.; final temperature: 300 ºC held for 7 minutes; detector temperature: 250 ºC.

Ligand screening

In a nitrogen-filled glove box, stock solution (0.1 M) of azetidinone **1** (1.1 equiv) in toluene was prepared along with decane as an internal standard in a clean and predried scintillation vial. The stock solution of alkyne **2** (1.5 equiv) in toluene was also prepared in a separate vial. In separate vials, stock solutions of catalyst were prepared by mixing $Ni(COD)_2$ and ligands (see Table 3.1 for the molar ratio). 10 mol % catalyst was added to the vial containing azetidinone and alkyne. The vials were taken out of the glove box and stirred @ 60 °C for overnight, after which all the reaction vials were opened to air and then analyzed by GC.

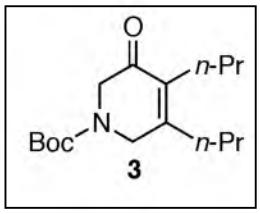
General procedure 'A' for cycloaddition

In a nitrogen-filled glove box, 5 mol % catalyst solution (prepared from $Ni(COD)_2$ and PPh_3 in 1:2 molar ratio in toluene) was added to the vial containing azetidinone (1 equiv, 0.1 M) and alkyne (1.5 equiv) in toluene. The vial was taken out of the glove box and stirred @ 60 °C for 6 h, opened to air, concentrated in vacuo, and purified by silica gel flash column chromatography.

General procedure 'B' for cycloaddition

In a nitrogen-filled glove box, 5 mol % catalyst solution (prepared from $Ni(COD)_2$ and PPh_3 in 1:2 molar ratio in toluene) was added to the vial (fitted with a PTFE septum) containing azetidinone (1 equiv, 0.1 M). The vial was taken out of the glove box and stirred @ 100 °C. Then solution of alkyne (3.0 equiv) in toluene was added to the vial containing azetidinone over a period of 2 h and stirred for another 4 h @ 100 °C, opened to air, concentrated in vacuo, and purified by silica gel flash column chromatography.

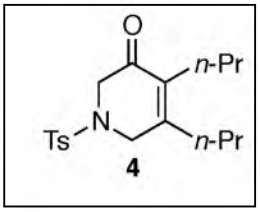
Tert-butyl 5-oxo-3,4-dipropyl-5,6-dihydropyridine-1(2H)-carboxylate (**3**)



3

The general procedure 'A' was used with 59.7 mg (0.35 mmol, 0.1 M) of azetidinone **1**, 57.6 mg (0.52 mmol) of 3-octyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford 95.1 mg of title compound **3** as a colorless oil, 97% yield. ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.10 (br, s, 2H), 4.01 (s, 2H), 2.24 (t, 4H, J = 6 Hz), 1.53 (sextet, 2H, J = 6 Hz), 1.44 (s, 9H), 1.33 (sextet, 2H, J = 6 Hz), 0.97 (t, 3H, J = 6 Hz), 0.89 (t, 3H, J = 6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.4, 156.2 (br), 154.3, 134.4, 80.8, 51.7 (br), 45.9 (br), 34.4, 28.5, 26.8, 22.7, 21.6, 14.44, 14.40. IR (CH_2Cl_2, cm^{-1}): 2964, 2873, 1704, 1677,1420, 1368, 1242, 1168, 1136, 905, 769. HRMS (ESI) calcd for $C_{16}H_{27}NO_3Na$ [M+Na]+ 304.1889, found 304.1892.

4,5-Dipropyl-1-tosyl-1,6-dihydropyridin-3(2H)-one (**4**)



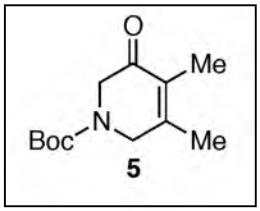
4

The general procedure 'A' was used with 20.4 mg (0.09 mmol, 0.1 M) of 1-tosyl-3-azetidinone, 15.0 mg (0.14 mmol) of 3-octyne, and 5 mol % of catalyst in toluene. The reaction mixture was

purified via flash column chromatography using 15% ethyl acetate in hexanes to afford 28.8 mg of title compound **4** as a colorless oil, 96% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (d, 2H, J = 6 Hz), 7.33 (d, 2H, J = 6 Hz), 3.86 (s, 2H), 0.97 (t, 3H, J = 6 Hz), 0.85 (t, 3H, J = 6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 191.4, 153.9, 144.4, 135.0, 133.1, 130.1, 127.9, 52.7, 48.0, 34.6, 26.7, 22.6, 21.7, 21.5, 14.5, 14.4. IR (CH_2Cl_2, cm-1): 2962, 2932, 2872, 1676, 1494, 1351, 1166, 1090, 1039, 963, 839, 815, 673, 582, 547. HRMS (ESI) calcd for $C_{18}H_{25}NO_3NaS$ [M+Na]+ 358.1477, found 358.1443.

Tert-butyl 3,4-dimethyl-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (**5**)

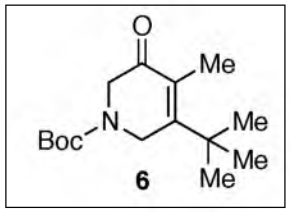


5

The general procedure 'A' was used with 28.1 mg (0.16 mmol, 0.1 M) of azetidinone **1**, 13.3 mg (0.25 mmol) of 2-butyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15-20% ethyl acetate in hexanes to afford 35.0 mg of title compound **5** as a colorless oil, 95% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.08 (s, 2H), 4.01 (s, 2H), 1.90 (s, 3H), 1.75 (s, 3H), 1.41(s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.1, 154.1, 152.5 (br), 129.9, 80.8, 51.2 (br), 47.3 (br), 28.4, 18.4, 10.2. IR (CH_2Cl_2, cm^{-1}): 2976, 2930, 1701, 1678, 1420, 1366, 1323, 1282,1243, 1172, 1136, 897, 856, 769. HRMS (ESI) calcd for $C_{12}H_{19}NO_3Na$ [M+Na]+ 248.1263,found 248.1256.

Tert-butyl 3-(tert-butyl)-4-methyl-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (**6**)



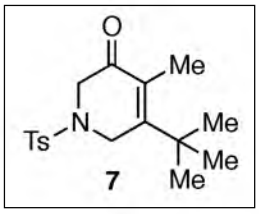
6

The general procedure 'A' was used with 28.0 mg (0.16 mmol, 0.1 M) of azetidinone **1**, 23.59 mg (0.25 mmol) of *tert*-

butyl-methyl alkyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford 40.6 mg of title compound **6** as a colorless oil, 93% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.21 (s, 2H), 4.01 (s, 2H), 1.96 (t, 3H, J = 3 Hz), 1.46 (s, 9H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 195.0, 162.6, 154.4, 130.5, 80.9, 51.0 (br), 44.9 (br), 29.2, 28.5, 13.4. IR (CH_2Cl_2, cm^{-1}): 2975, 1679, 1606, 1429, 1370, 1252, 1167, 1128, 1074, 1040, 911, 856, 770. HRMS (ESI) calcd for $C_{15}H_{25}NO_3Na$ [M+Na]+ 290.1732, found 290.1738.

5-(Tert-butyl)-4-methyl-1-tosyl-1,6-dihydropyridin-3(2H)-one (7)

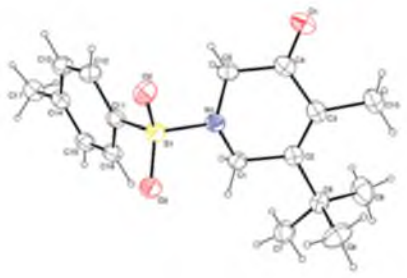


7

The general procedure 'A' was used with 21.1 mg (0.09 mmol, 0.1 M) of 1-tosyl-3-azetidinone, 13.51 mg (0.14 mmol) of *tert*-butyl-methyl alkyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 20% ethyl acetate in hexanes to afford the title compound **7** as a colorless solid, 77% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (d, 2H, J = 8 Hz), 7.33 (d, 2H, J = 8 Hz), 3.95 (s, 2H), 3.72 (s, 2H), 2.42 (s, 3H), 1.81 (t, 3H, J = 1.6 Hz), 1.22 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.8, 159.7, 144.3, 133.3, 131.2, 130.1, 127.9, 52.2, 47.0, 37.1, 29.1, 21.7, 13.2. IR (CH_2Cl_2, cm^{-1}): 2969, 2868, 2824, 1674, 1598, 1444, 1348, 1165, 1089, 1036, 1007, 959, 665, 580, 547. HRMS (ESI) calcd for $C_{17}H_{23}NO_3NaS$ [M+Na]+ 344.1296, found 344.1307.

The crystals suitable for X-ray crystallographic analysis were grown using tetrahydrofuran and hexanes as solvents.

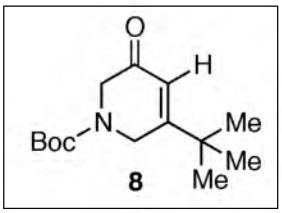


Crystal data and structure refinement for **7**

Empirical formula	$C_{17}H_{23}NO_3S$	
Formula weight	321.42	
Temperature	150(1) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	***P*** $2_1/a$	
Unit cell dimensions	a = 8.7602(13) Å	a= 90°.
	b = 19.148(3) Å	b= 110.824(11)°.
	c = 10.7909(16) Å	g = 90°.
Volume	1691.8(5) $Å^3$	
Z	4	
Density (calculated)	1.262 Mg/m^3	
Absorption coefficient	0.203 mm^{-1}	
F(000)	688	
Crystal size	0.35 x 0.30 x 0.15 mm^3	
Theta range for data collection	2.28 to 27.52°	
Index ranges	-11<=h<=11, -20<=k<=24, -14<=l<=13	
Reflections collected	5667	

Independent reflections	3694 [R(int) = 0.0326]
Completeness to theta = 25.00^{c}	96.9 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9702 and 0.9323
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3694 / 0 / 237
Goodness-of-fit on F^2	1.116
Final R indices [I>2sigma(I)]	R1 = 0.0629, wR2 = 0.1321
R indices (all data)	R1 = 0.1173, wR2 = 0.1638
Extinction coefficient	0.042(5)
Largest diff. peak and hole	0.268 and -0.398 e.Å^{-3}

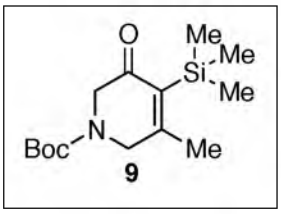
Tert-butyl 3-(tert-butyl)-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (**8**)



8

The general procedure 'B' was used with 23.0 mg (0.13 mmol, 0.2 M) of azetidinone **1**, 33.10 mg (0.40 mmol) of *tert*-butylacetylene, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 20% ethyl acetate in hexanes to afford title compound **8** as colorless oil, 71% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.04 (t, 1H, J = 1.6 Hz), 4.22 (s, 2H), 4.02 (s, 2H), 1.46 (s, 9H), 1.18 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.8, 154.4, 121.7, 81.0, 51.4 (br), 42.8 (br), 36.3, 28.5. IR (CH_2Cl_2, cm^{-1}): 2971, 2875, 1701, 1683, 1620, 1477, 1418, 1367, 1236, 1165, 1112, 903, 884, 854, 767. HRMS (ESI) calcd for $C_{14}H_{23}NO_3Na$ [M+Na]+ 276.1576, found 276.1581.

Tert-butyl 3-methyl-5-oxo-4-(trimethylsilyl)-5,6-dihydropyridine-1(2H)-carboxylate (**9**)



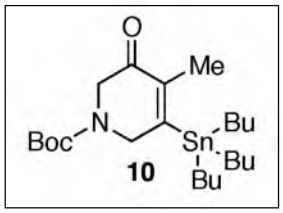
9

The general procedure 'A' was used with 41.9 mg (0.25 mmol, 0.1 M) of azetidinone **1**, 41.2 mg (0.37 mmol) of trimethylsilyl-methyl alkyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 10-15% ethyl acetate in hexanes to afford 63.8 mg (55 mg major regioisomer, 4.4 mg minor regioisomer, and 4.4 mg mixture of both regioisomers) of title compound **9** as a colorless oil, 92% yield.

^{1}H NMR (400 MHz, $CDCl_3$): (major isomer) δ (ppm) 4.03 (s, 2H), 3.94 (s, 2H), 2.03 (s, 3H), 1.46 (s, 9H), 0.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 197.1, 166.2 (br), 154.3, 135.5, 80.9, 51.3 (br), 48.3 (br), 28.5, 21.8, 1.3. IR (CH_2Cl_2, cm^{-1}): 2976, 2901, 2824, 1700, 1664, 1596, 1477, 1418, 1365, 1245, 1161, 1116, 1054, 945, 899, 845, 765, 691. HRMS (ESI) calcd for $C_{14}H_{25}NO_3NaSi$ [M+Na]+ 306.1501, found 306.1506.

^{1}H NMR (400 MHz, $CDCl_3$): (minor isomer) δ (ppm) 4.22 (s, 2H), 4.08 (s, 2H), 1.94 (t, 3H, J = 2.1 Hz), 1.48 (s, 9H), 0.28 (s, 9H).

Tert-butyl 4-methyl-5-oxo-3-(tributylstannyl)-5,6-dihydropyridine-1(2H)-carboxylate (**10**)



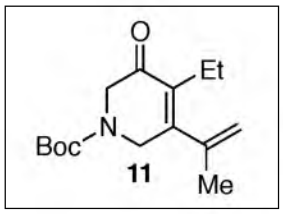
10

The general procedure 'A' was used with 23.1 mg (0.13 mmol, 0.2 M) of azetidinone **1**, 66.61 mg (0.20 mmol) of tributylstannyl-methyl alkyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 5 to 10% ethyl acetate in hexanes to afford 60.6 mg of title compound **10** as a colorless oil,

89% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.06 (s, 2H), 4.00 (s, 2H), 2.01 (t, 3H, J = 2.5 Hz), 1.47 (m, 16H), 1.30 (sextet, 6H, J = 3 Hz), 1.09 (m, 1H), 1.01 (m, 5H), 0.94 (m, 1H), 0.88 (m, 5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 197.1, 166.9 (br), 154.4, 139.4 (br), 80.9, 50.7 (br), 48.04 (br), 29.29, 28.54, 27.5, 23.66, 13.86, 11.74. IR (CH_2Cl_2, cm^{-1}): 2957, 2926, 2854, 1704, 1658, 1601, 1416, 1368, 1240, 1160, 1109, 1076, 895, 771, 670, 597. HRMS (ESI) calcd for $C_{23}H_{43}NO_3NaSn$ [M+Na]+ 524.2163, found 524.2185.

Tert-butyl 4-ethyl-5-oxo-3-(prop-1-en-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (**11**)



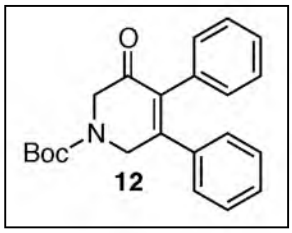
The general procedure 'A' was used with 39.7 mg (0.23 mmol, 0.2 M) of azetidinone **1**, 32.75 mg (0.35 mmol) of 2-methylhex-1-en-3-yne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford 40.6 mg of title compound **11** as a colorless oil, 87% yield.

^{1}H NMR (400 MHz, $CDCl_3$): (major isomer) δ (ppm) 5.13 (q, 1H, J = 1.2 Hz), 4.86 (s, 1H), 4.15 (s, 2H), 4.06 (s, 2H), 2.27 (q, 2H, J = 7.6 Hz), 1.93 (m, 3H), 1.46 (s, 9H), 0.97 (t, 3H, J = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.7, 156.5 (br), 154.3, 141.4, 134.7, 115.4, 81.0, 51.8 (br), 45.8 (br), 28.5, 22.1, 19.6, 14.5. IR (CH2Cl2, cm-1): 3083, 2975, 2934, 2876, 1702, 1681, 1621, 1417, 1368, 1238, 1169, 1129, 905, 866, 768. HRMS (ESI) calcd for $C_{15}H_{23}NO_3Na$ [M+Na]+ 288.1576, found 288.1580.

^{1}H NMR (400 MHz, $CDCl_3$): (minor isomer) δ (ppm) 5.22 (q, J = 1.8 Hz, 1H), 4.75 (m, 1H), 4.21(s, 2H), 4.09 (s, 2H), 2.33 (q, J = 7.5 Hz, 2H), 1.86 (m, 3H), 1.49 (s, 9H), 1.14

(t, J = 7.5 Hz, 3H).

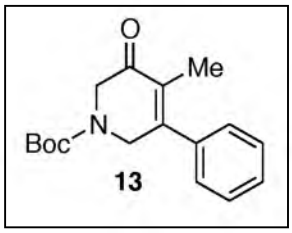
Tert-butyl 5-oxo-3,4-diphenyl-5,6-dihydropyridine-1(2H)-carboxylate (**12**)



The general procedure 'B' was used with 22.5 mg (0.13 mmol, 0.2 M) of azetidinone **1**, 70.27 mg (0.39 mmol) of diphenylacetylene, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 20-30% ethyl acetate in hexanes to afford 36.3 mg of the title compound **12** as pale oil, 79% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.19 (m, 6H), 7.11 (m, 2H), 7.00 (m, 2H), 4.6 (2H), 4.33 (s, 2H), 1.54 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 192.7, 154.4, 137.2, 136.1 (br), 133.8, 131.0, 129.0, 128.7, 128.4, 127.9, 127.5, 81.4, 52.1 (br), 47.9 (br), 28.6. IR (CH_2Cl_2, cm^{-1}): 3059, 2979, 2932, 1760, 1696, 1479, 1413, 1368, 1326, 1243, 1157, 1115, 993, 931, 858, 762, 737, 699. HRMS (ESI) calcd for $C_{22}H_{23}NO_3Na$ [M+Na]+ 372.1576, found 372.1583.

Tert-butyl 4-methyl-5-oxo-3-phenyl-5,6-dihydropyridine-1(2H)-carboxylate (**13**)

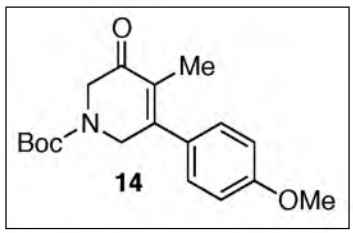


The general procedure 'B' was used with 20.8 mg (0.12 mmol, 0.2 M) of_azetidinone **1**, 42.34 mg (0.25 mmol) of phenyl-methyl alkyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford 28.2 mg of the title compound **13** as a colorless oil, 81% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 (m, 3H), 7.28 (d, 2H, J = 6.8 Hz), 4.41 (s, br, 2H), 4.20 (s, 2H), 1.78 (t, 3H, J = 1.7 Hz), 1.49 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.3, 154.3, 137.4, 130.8 (br), 129.1, 128.8, 128.2, 127.8, 81.1, 51.7 (br), 47.6 (br), 28.5, 12.3. IR (CH_2Cl_2, cm^{-1}): 3059, 2929, 1699, 1632, 1476, 1418, 1327, 1281, 1244, 1120, 1069, 1032, 1000, 897, 861, 765, 702, 623. HRMS (ESI) calcd for $C_{17}H_{21}NO_3Na$ [M+Na]+ 310.1419, found 310.1422.

Tert-butyl 3-(4-methoxyphenyl)-4-methyl-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (**14**)

The general procedure 'B' was used with 32.9 mg (0.19 mmol, 0.2 M) of azetidinone **1**, 78.48 mg (0.57 mmol) of *p*-methoxyphenyl-methyl alkyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 20% ethyl acetate in hexanes to afford 48.5 mg of title compound **14** as pale yellow oil, 74% yield.



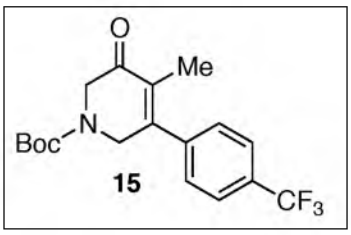
14

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23 (d, 2H, J = 8.4 Hz), 6.94 (d, 2H, J = 8.8 Hz), 4.39 (s, 2H), 4.16 (s, 2H), 3.83 (s, 2H), 1.79 (t, 3H, J = 1.8 Hz), 1.47 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.4, 160.3, 154.3, 130.3, 129.6, 129.4, 55.5, 51.6 (br), 47.6 (br), 28.5, 12.5. IR (CH_2Cl_2, cm^{-1}): 2976, 2932, 2838, 1698, 1677, 1608, 1512, 1417, 1365, 1250, 1170, 1119, 1033, 945, 834, 768. HRMS (ESI) calcd for $C_{18}H_{23}NO_4Na$ [M+Na]+ 340.1525, found 340.1530.

Tert-butyl 4-methyl-5-oxo-3-(4-(trifluoromethyl)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate (**15**)

The general procedure 'B' was used with 39.1 mg (0.23 mmol, 0.2 M) of azetidinone

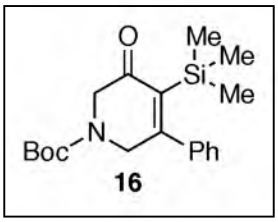
1, 126.18 mg (0.68 mmol) of *p*-trifluoromethylphenyl-methyl alkyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 20% ethyl acetate in hexanes to afford title compound **15** as a colorless oil, 63% yield.[18]



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.69 (d, 2H, *J* = 8.4 Hz), 7.39 (d, 2H, *J* = 8.0 Hz), 4.38 (s, 2H), 4.20 (s, 2H), 1.74 (t, 3H, *J* = 2Hz), 1.48 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 193.9, 154.2, 141.0, 131.3 (t, *J* = 35 Hz), 128.3, 125.9 (q, *J* = 15.2 Hz), 125.3, 122.6, 81.4, 51.6, 47.5, 28.5, 12.2. IR (CH_2Cl_2, cm^{-1}): 2980, 2933, 1687, 1617, 1477, 1408, 1367, 1325, 1281, 1244, 1167, 1127, 1068, 1019, 998, 900, 844, 768, 686, 613. HRMS (ESI) calcd for $C_{18}H_{20}NO_3F_3Na$ [M+Na]+ 378.1293, found 378.1292.

Tert-butyl 5-oxo-3-phenyl-4-(trimethylsilyl)-5,6-dihydropyridine-1(2H)-carboxylate (**16**)

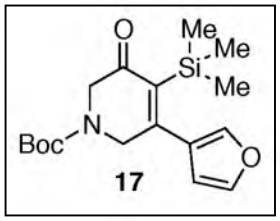
The general procedure 'B' was used with 29.3 mg (0.17 mmol, 0.2 M) of azetidinone **1**, 89.47 mg (0.51 mmol) of trimethylsilyl-phenyl alkyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 10-15% ethyl acetate in hexanes to afford 48.5 mg of title compound **16** as a colorless oil, 82% yield.



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41 (m, 3H), 7.28 (m, 2H), 4.32 (s, 2H), 4.09 (s, 2H), 1.51 (s, 9H), -0.12 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 198.0, 168.6 (br), 154.4, 139.5, 137.7, 129.6, 128.6, 128.1, 81.1, 51.7 (br), 49.2 (br), 28.6, 0.5. IR (CH2Cl2, cm-1): 2977, 2899, 1702, 1669, 1582, 1478, 1412, 1365, 1246, 1164, 1115, 1044, 1000,

939, 905, 845, 762, 700. HRMS (ESI) calcd for $C_{19}H_{27}NO_3NaSi$ [M+Na]+ 368.1658, found 368.1661.

Tert-butyl 3-(furan-3-yl)-5-oxo-4-(trimethylsilyl)-5,6-dihydropyridine-1(2H)-carboxylate (**17**)

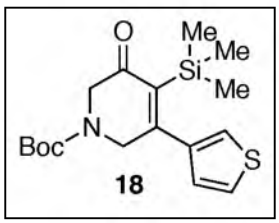


17

The general procedure 'B' was used with 32.0 mg (0.18 mmol, 0.2 M) of azetidinone **1**, 92.1 mg (0.56 mmol) of trimethylsilyl-3-furanyl alkyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 10-15% ethyl acetate in hexanes to afford 51.1 mg of title compound **17** as a colorless oil, 82% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 (m, 2H), 6.48 (s, 1H), 4.24 (s, br, 2H), 4.06 (s, 2H), 1.49 (s, 9H), 0.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 198.0, 158.8 (br), 154.4, 143.9, 141.7, 137.8, 124.3, 110.9, 81.2, 51.9 (br), 48.2 (br), 28.5, 0.9. IR (CH_2Cl_2, cm^{-1}): 2978, 1701, 1668, 1591, 1414, 1366, 1246, 1162, 1018, 939, 845, 766, 600. HRMS (ESI) calcd for $C_{17}H_{25}NO_4NaSi$ [M+Na]+ 358.1451, found 358.1447.

Tert-butyl 5-oxo-3-(thiophen-3-yl)-4-(trimethylsilyl)-5,6-dihydropyridine-1(2H)-carboxylate (**18**)

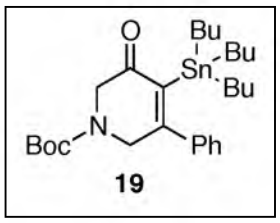


18

The general procedure 'B' was used with 25.6 mg (0.15 mmol, 0.2 M) of azetidinone **1**, 80.90 mg (0.45 mmol) of trimethylsilyl-3-thiophenyl alkyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 15% ethyl acetate in hexanes to afford 42.2 mg of title compound **18** as slightly pale oil, 80% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 (m, 1H), 7.28 (s, 1H), 7.09 (d, 1H, J = 4 Hz), 4.30 (s, 2H), 4.07 (s, 2H), 1.49 (s, 9H), -0.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 198.1, 162.7 (br), 154.4, 140.0, 138.1, 127.8, 126.7, 125.6, 81.1, 51.7 (br), 48.7 (br), 28.5, 0.5. IR (CH_2Cl_2, cm^{-1}): 2977, 1701, 1666, 1578, 1411, 1366, 1246, 1163, 1116, 1048, 930, 844, 766, 695. HRMS (ESI) calcd for $C_{17}H_{25}NO_3NaSSi$ [M+Na]+ 374.1222, found 374.1227.

Tert-butyl 5-oxo-4-phenyl-3-(tributylstannyl)-5,6-dihydropyridine-1(2H)-carboxylate (**19**)



19

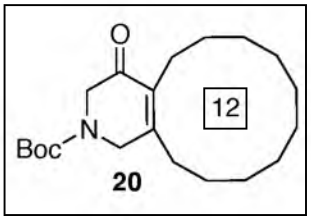
The general procedure 'B' was used with 22.9 mg (0.13 mmol, 0.2 M) of azetidinone **1**, 78.48 mg (0.20 mmol) of tributylstannyl-phenyl alkyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 10-15% ethyl acetate in hexanes to afford 48.5 mg of title compound **19** as pale oil, 82% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 (m, 3H), 7.29 (m, 2H), 4.38 (s, 2H), 4.14 (s, 2H), 1.51 (s, 9H), 1.29 (m, 6H), 1.18 (m, 6H), 0.82 (t, 9H, J = 7.2 Hz), 0.63 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 197.7, 169.0 (br), 154.5, 141.7 (br), 140.4, 129.5, 128.8, 127.7, 81.0, 51.3 (br), 48.5 (br), 29.1, 28.5, 27.4, 13.8, 11.5. IR (CH_2Cl_2, cm^{-1}): 2956, 2924, 2871, 2853, 1703, 1660, 1583, 1415, 1365, 1265, 1239, 1164, 1110, 760, 699. HRMS (ESI) calcd for $C_{28}H_{45}NO_3NaSn$ [M+Na]+ 586.2319, found 586.233.

Tert-butyl 4-oxo-3,4,5,6,7,8,9,10,11,12,13,14-dodecahydrocyclo dodeca[*c*]pyridine-2(1*H*)-carboxylate (**20**)

The general procedure 'A' was used with 45.3 mg (0.26 mmol, 0.2 M) of azetidinone

1, 65.2 mg (0.39 mmol) of cyclododecyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 10-15% ethyl acetate in hexanes to afford title compound **19** as a colorless oil, 96% yield.

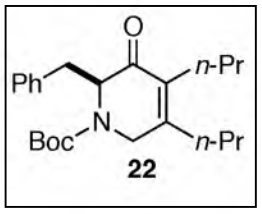


20

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.12 (s, 2H), 4.02 (s, 2H), 2.32 (m, 4H), 1.7-1.2 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 197.1, 167.1 (br), 154.4, 139.4 (br), 80.9, 50.7 (br), 48.0 (br), 29.3, 29.29, 29.2, 28.5, 27.8, 27.4, 27.1, 23.6, 13.8, 11.7. IR (CH_2Cl_2, cm^{-1}): 2861, 2361, 1676, 1626, 1469, 1419, 1325, 1281, 1138, 1066, 1032. HRMS (ESI) calcd for $C_{20}H_{33}NO_3Na$ [M+Na]+ 358.2358, found 358.2350.

Tert-butyl 6-benzyl-5-oxo-3,4-dipropyl-5,6-dihydropyridine-1(2H)-carboxylate (**22**)

The general procedure 'A' was used with 24.0 mg (0.09 mmol, 0.2 M) of 1-Boc-2-benzyl-3-azetidinone,[19] 15.18 mg (0.13 mmol) of 3-octyne, and 5 mol % of catalyst in toluene. The reaction mixture was purified via flash column chromatography using 10% ethyl acetate in hexanes to afford the title compound **22** as pale yellow oil, 88% yield, >99% ee ($[\alpha]_D^{20}$ = -27.6 (c = 0.44, $CHCl_3$)).

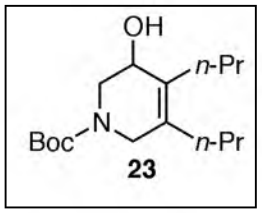


22

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.26 (m, 3H), 7.13 (d, 2H, J = 8.8 Hz), 4.7 (dd, 1H, J = 5.6 Hz), 4.60 (d, 1H), 3.70 (d, 1H), 2.85 (m, 2H), 2.25 (m, 4H), 1.52 (sextet, 2H, J = 10.0 Hz), 1.43-1.15 (m, 1H), 0.97 (t, 3H, J = 9.6 Hz), 0.93 (t, 3H, J = 9.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 195.4, 155.4, 154.2, 137.3, 133.2, 129.7, 128.7, 126.8, 80.5, 61.7, 43.4, 37.2, 34.4, 28.1, 27.0, 22.7, 21.8, 14.5, 14.4. IR (CH_2Cl_2, cm^{-1}): 3063, 3028,

2963, 2932, 2872, 1697, 1672, 1635, 1495, 1454, 1415, 1368, 1315, 1280, 1243, 1169, 1131, 1030, 976, 949, 878, 762, 700. HRMS (ESI) calcd for $C_{23}H_{33}NO_3Na$ [M+Na]+ 394.2358, found 394.2358.

Tert-butyl 5-hydroxy-3,4-dipropyl-5,6-dihydropyridine-1(2H)-carboxylate (**23**)



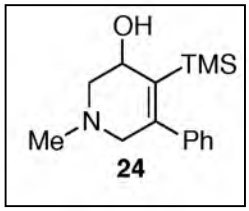
23

The general procedure 'A' was used with 51.9 mg (0.30 mmol, 0.2 M) of azetidinone **1**, 50.11 mg (0.45 mmol) of 3-octyne, and 5 mol % of catalyst in toluene. After the completion of reaction, solvent was evaporated and the residue was dissolved in MeOH (0.1 M). To the resulting solution was added $CeCl_3 \cdot 7H_2O$ (0.55 equiv), then it was cooled to -78 °C and sodium borohydride (1.1 equiv) was carefully added to it. The resulting solution was allowed to warm to room temperature. The reaction was carefully quenched; the product was extracted with EtOAc and dried over anhydrous MgSO4. The residue was purified via flash column chromatography using 30-50% EtOAc in hexanes to afford title compound **23** as a colorless oil, 94% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.97 (m, 3H), 3.5 (d, 1H), 3.04 (d, 1H), 2.12 (t, 2H, *J* = 3 Hz), 1.95 (m, 2H), 1.45 (s, 9H), 1.39 (m, 4H), 0.9 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 155.8, 132.2, 80.0, 66.2, 48.7 (br), 46.3 (br), 32.6, 31.8, 28.5, 24.1, 22.0, 14.47, 14.41. HRMS (ESI) calcd for $C_{16}H_{29}NO_3Na$ [M+Na]+ 306.2045, found 306.2057.

1-Methyl-5-phenyl-4-(trimethylsilyl)-1,2,3,6-tetrahydropyridin-3-ol (**24**)

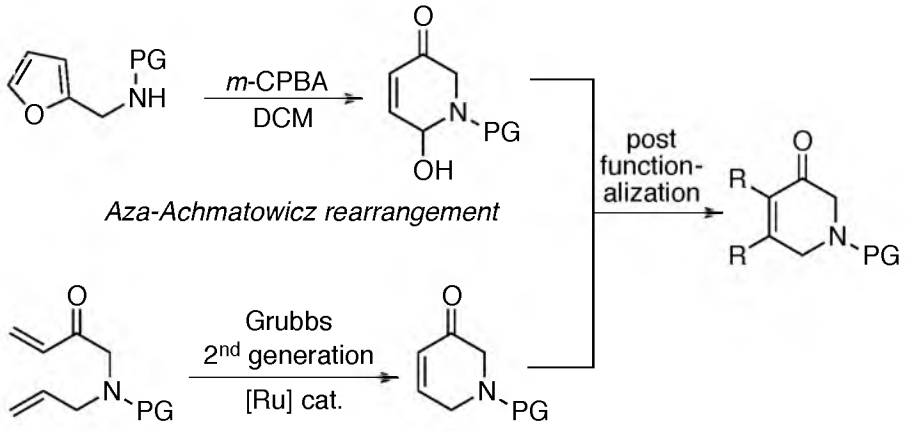
The general procedure 'B' was used with 33.5 mg (0.19 mmol, 0.2 M) of azetidinone **1**, 78.48 mg (0.58 mmol) of trimethylsilyl-phenyl alkyne, and 5 mol % of catalyst in



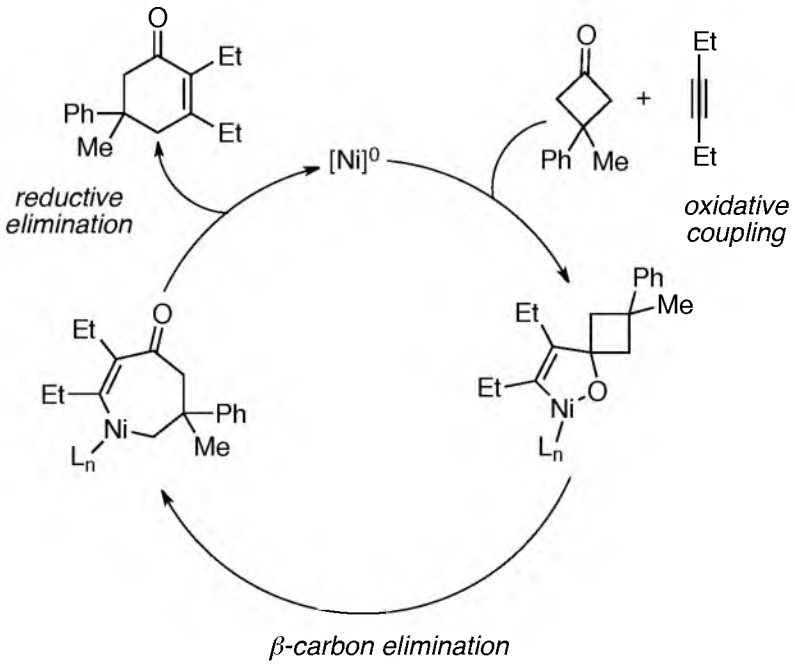
24

toluene. After the completion of reaction, solvent was evaporated and the residue was dissolved in ether (0.1 M). The resulting solution was cooled to 0 °C and lithium aluminum hydride (10 equiv) was carefully added to it. The resulting suspension was allowed to warm to room temperature, and stirred overnight. The reaction was carefully quenched; the product was extracted with EtOAc and dried over anhydrous $MgSO_4$. The residue was purified via flash column chromatography using 10% MeOH in DCM to afford title compound **24** as a colorless oil, 51% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.28 (m, 3H), 7.13 (dd, 2H, *J* = 2H), 4.27 (t, 1H, *J* = 4Hz), 3.18 (d, 1H), 2.9 (d, 1H), 2.80 (dd, 1H, *J* = 3.2, 8.0 Hz), 2.46 (dd, 1H, *J* = 3.2 Hz, 8.0 Hz), 2.36 (s, 3H), 0.15 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 150.4, 142.3, 135.1, 128.5, 128.1, 127.6, 67.3, 62.0, 59.9, 45.5, 0.4. IR (CH_2Cl_2, cm^{-1}): 3446, 3053, 2947, 2922, 2843, 2770, 1620, 1594, 1456, 1242, 1114, 1083, 1059, 998, 887, 838, 761, 702. HRMS (ESI) calcd for $C_{15}H_{24}NOSi$ [M+H]+ 262.1627, found 262.1630.



Scheme 3.1 Existing strategies to 3-piperidones

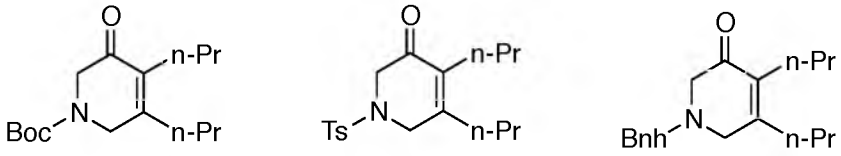


Scheme 3.2 Proposed mechanism

Table 3.1 Ni-catalyzed [4+2] cycloaddition[a]

Entry	Ligand (L_n)	Conv. (%)[b]	Yield (%)[c]
1	PBu_3	>99	55
2	PCy_3	>99	72
3	P(*t*-Bu)$_3$	>99	41
4	**PPh_3**	**>99**	**94**
5	P(*o*-tol)$_3$	>97	54
6	P(*p*-tol)$_3$	>99	74
7	DPPE	37	12
8	DCPE	50	5
9	*rac*-BINAP	>99	82
10	DPPF	>99	80
11	DPPB	>99	81

[a]Reaction conditions: azetidinone **1** (1 equiv), alkyne **2** (1.5 equiv), 10 mol % $Ni(COD)_2$, 20 mol % ligand for entries 1-6 and 10 mol % for entries 7-11.[b]Conversion of azetidinone **1** was determined by GC using decane as internal standard. [c]Determined by GC using decane as an internal standard.



3, 97% **4**, 96% N.R.

Figure 3.1 Investigation of protecting groups on "N" of azetidinones. Reaction conditions: azetidinone (1 equiv, 0.2 M), 3-octyne (1.5 equiv), 6 h. Isolated yields.

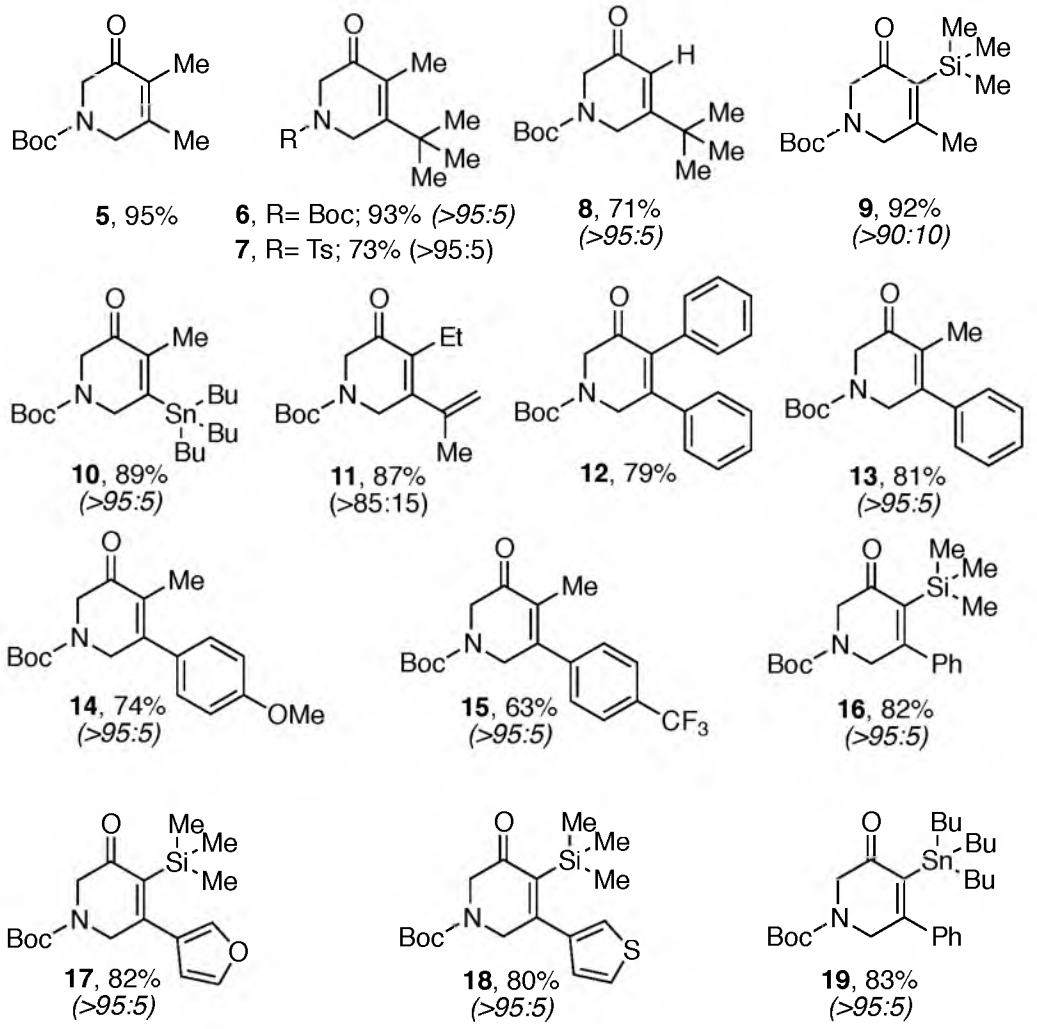


Figure 3.2 Ni-catalyzed coupling of azetidinone and alkynes. Method A (for **5-11** except **10**): 5 mol % $Ni(COD)_2$, 10 mol % PPh_3, toluene, 60 °C, azetidinone (2 equiv, 0.2 M), alkyne (1.5 equiv). Method B (for **10**, **12-19**): 5 mol % $Ni(COD)_2$, 10 mol % PPh_3, toluene, 100 °C, azetidinone (1 equiv, 0.2 M), alkyne (3.0 equiv and slow addition). Isolated yield. Regioselectivity (denoted in parentheses) was calculated by ^{1}HNMR of crude reaction mixture.

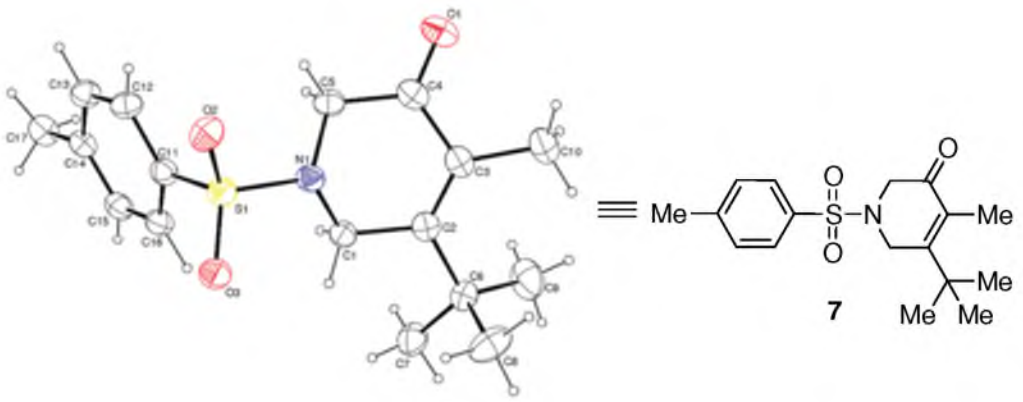
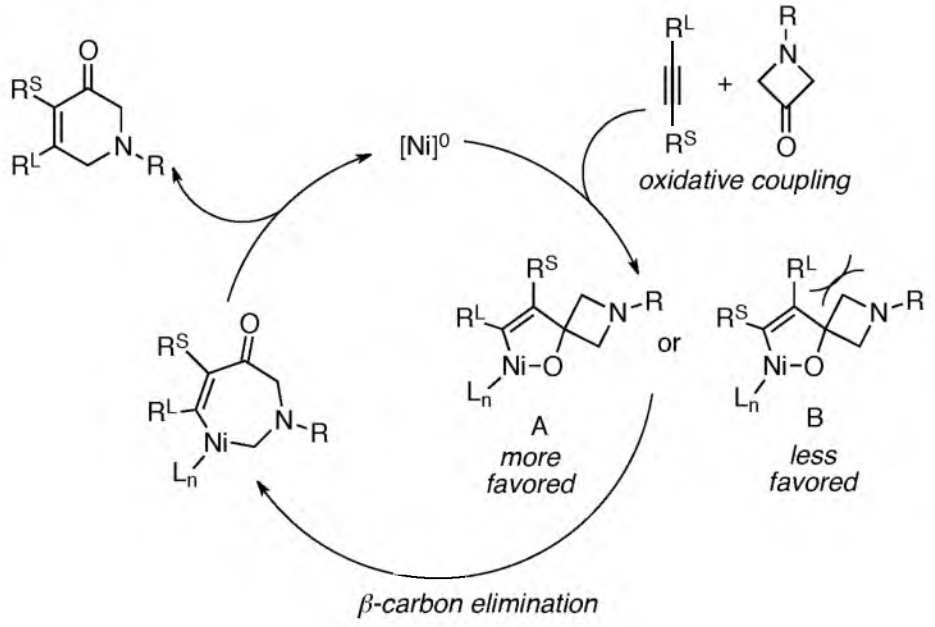
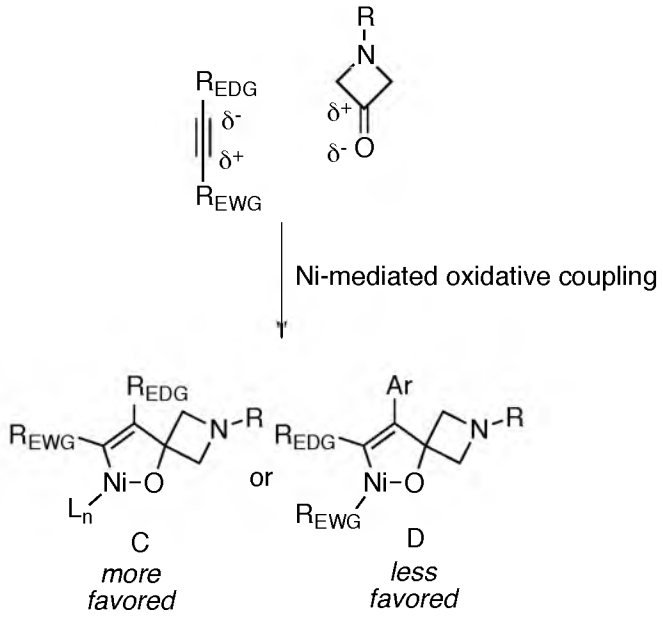


Figure 3.3 Ortep diagram of **7**



Scheme 3.3 Proposed mechanism of Ni-catalyzed [4+2] cycloaddition



Scheme 3.4 Proposed oxidative coupling products in electronically influenced alkynes

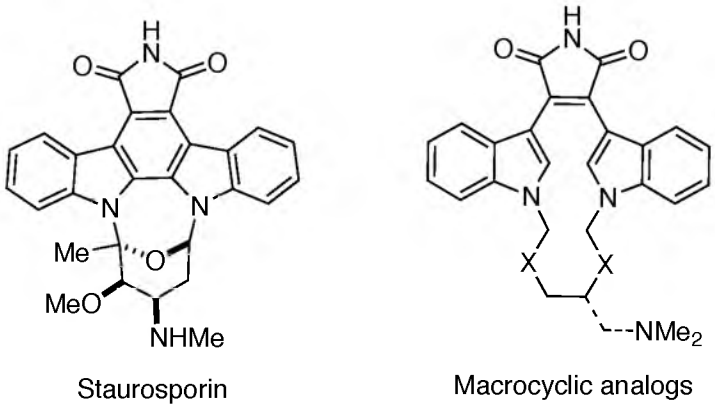
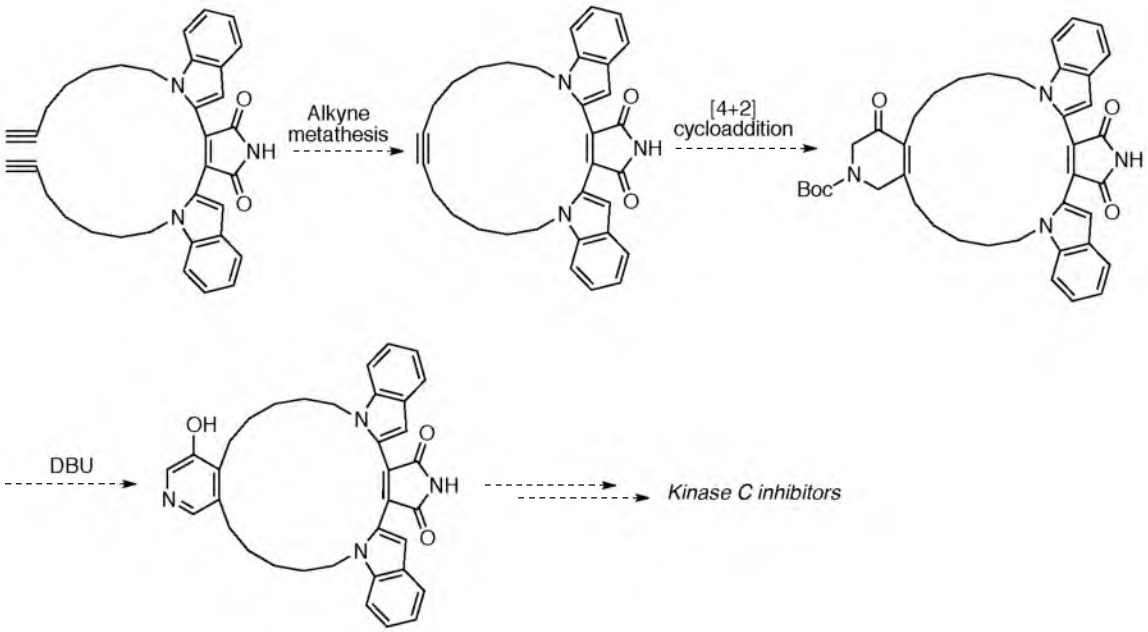


Figure 3.4 Staurosporin and its proposed macrocyclic analog



Scheme 3.5 Future work towards Kinase C inhibitors

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(18) The product was contaminated with small amount of 3-Boc-azetidinone (only visible by ^{1}HNMR, see spectrum).

(19) The 1-Boc-2-benzyl-3-azetidinone was prepared using known procedure. Boc-Phe-OH was converted to diazoketone using $TMSCHN_2$. See, Cesar, J.; Dollenc, M. S. *Tet. Lett.* **2001**, *42*, 7099. Notably, the yields were not reproducible and were only moderate (30-35 %) in our hands. The diazoketone was converted to the desired azetidinone using Seebach's protocol. See, Podlech, J.; Seebach, D. *Helv. Chim. Acta* **1995**, *78*, 1238.

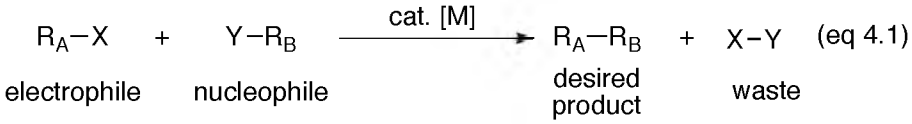
CHAPTER 4

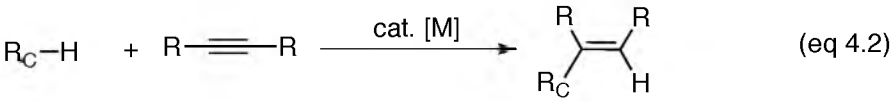
AN EXPEDITIOUS ROUTE TO EIGHT-MEMBERED HETEROCYCLES BY NICKEL-CATALYZED CYCLOADDITION: LOW TEMPERATURE C-C BOND CLEAVAGE

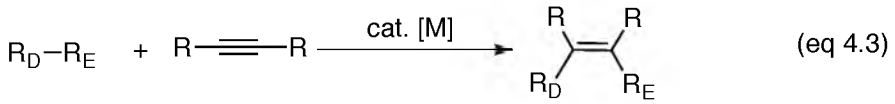
Introduction

Be it the design of a simple or architecturally complex molecule, carbon–carbon bond formation processes play a pivotal role. One of the most common adopted strategies to accomplish these tasks is the cross-coupling reaction, where electrophiles and nucleophiles are coupled with the aid of a suitable transition-metal catalyst (eq 4.1).[1] However, a limitation of cross-coupling methods is the amount of waste being produced in these processes.[1] One solution is the use of less oxidized substrates like arenes or alkanes, which would be coupled through selective C-H functionalizations.[2] In the 21st century, chemists have witnessed immense growth in the field of C-H bond activation, which represents an elegant method for constructing C-C bonds in a manner that minimizes waste (eq 4.2).[3] Alternatively, C-C bond activation provides another possible solution (eq 4.3). Although significant progress has been made in the area of C-H bond activation, C-C bond activation is still in its infancy.[4] The paucity of developments in this area can be attributed to the highly inert nature of the C-C σ-bond

and the poor interaction of the orbitals of C-C σ-bonds with transition metals.[4]

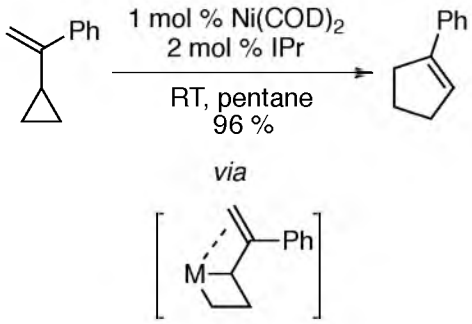




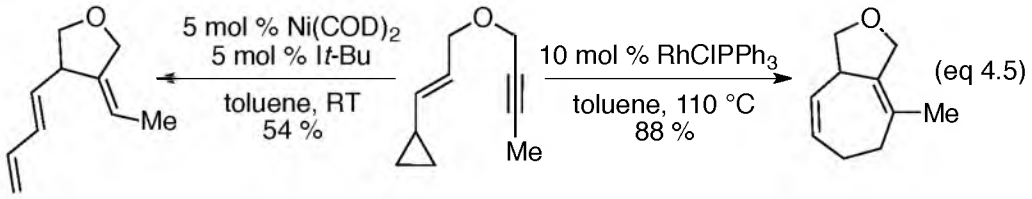


There is a significant body of literature that describes the use of the inherent strain of cyclopropanes (strain energy = 27.6 kcal mol^{-1}) in transition-metal-catalyzed reactions.[5] More specifically, Wender and coworkers have demonstrated that placing an alkene moiety next to cyclopropane assists in coordination with transition metal. This initial coordination with the metal promotes oxidative addition of the cyclopropane ring, which later rearranges to cyclpentenes. This idea has also been successfully exploited by Louie and coworkers (eq 4.4). Taking advantage of this concept, the authors were able to couple the oxidative addition product with alkyne. When cyclopropyl enynes were subjected to Ni/IPr catalyst system, formation of a skipped triene product was observed (eq 4.5). Wender and coworkers observed that a Rh-catalyst affords a bicyclic product instead of a skipped triene (eq 4.5). Moreover, in comparison to cyclopropanes, the use of cyclobutanes (strain energy = 26.4 kcal mol^{-1}) in such reactions remained largely unexplored until the finding of Ito, which utilized stoichiometric amount of Wilkinson catalyst to oxidatively add the four-membered ketone (eq 4.6).[6] Since then, appreciable

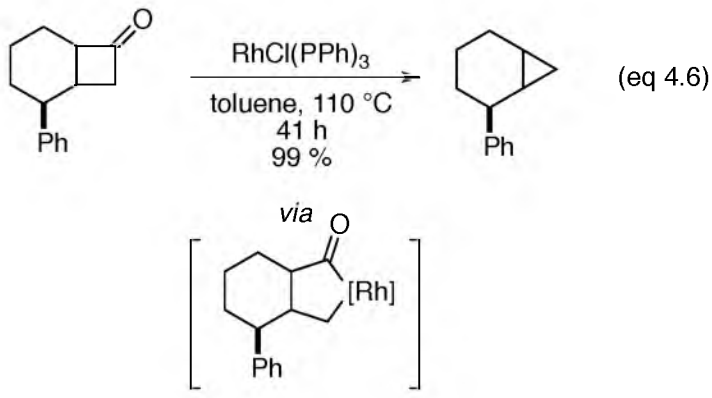
efforts have been made in using various transition-metal catalysts to harness the latent potential of cyclobutanones.[7] Murakami has successfully exploited the ring strain of cyclobutanone in an intrameolcular coupling with an alkene (eq 4.7) and alkyne (eq 4.8). Similarly, Rh-catalyst has also been found to promote the ring opening of vinyl cyclobutanone and then subsequent coupling with pendant alkene affords an eight-memebred carbocycle (eq 4.9). Notably, most of these studies focused on the development of methods for accessing carbocycles that were, at the time, difficult to synthesize.



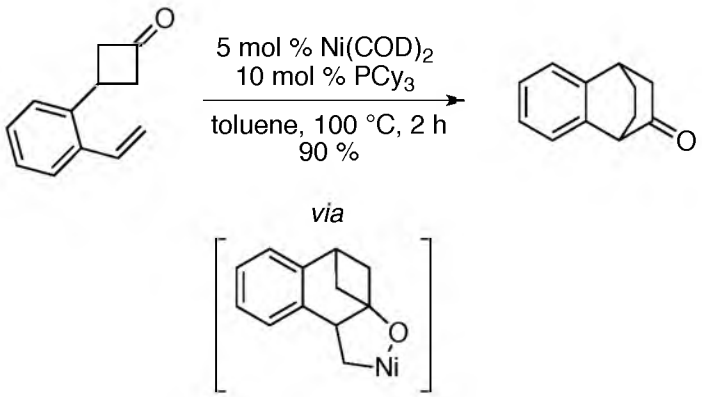
(eq 4.4)



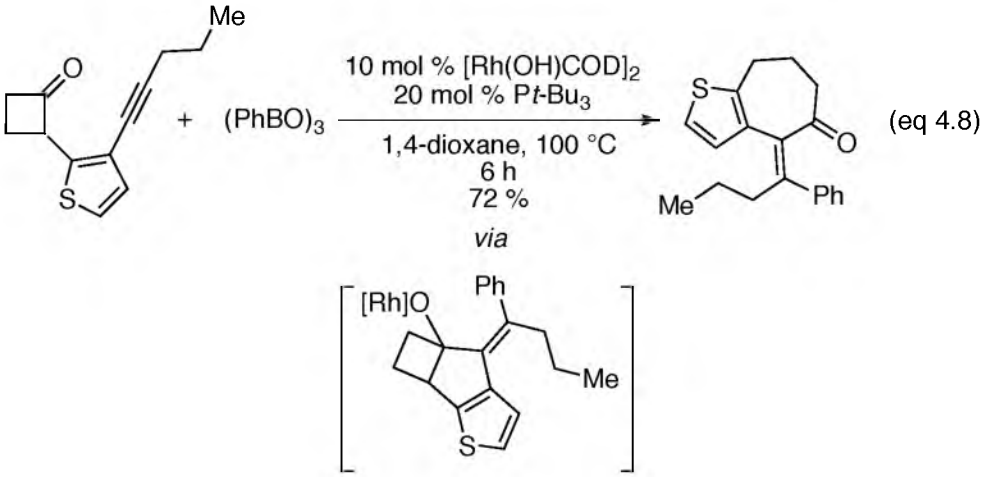
(eq 4.5)



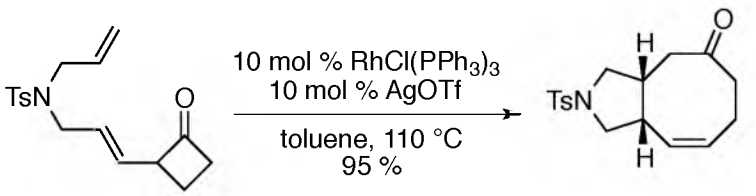
(eq 4.6)



(eq 4.7)

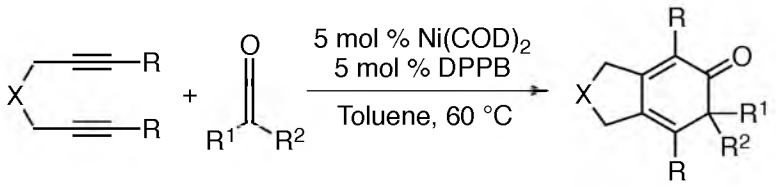


(eq 4.8)

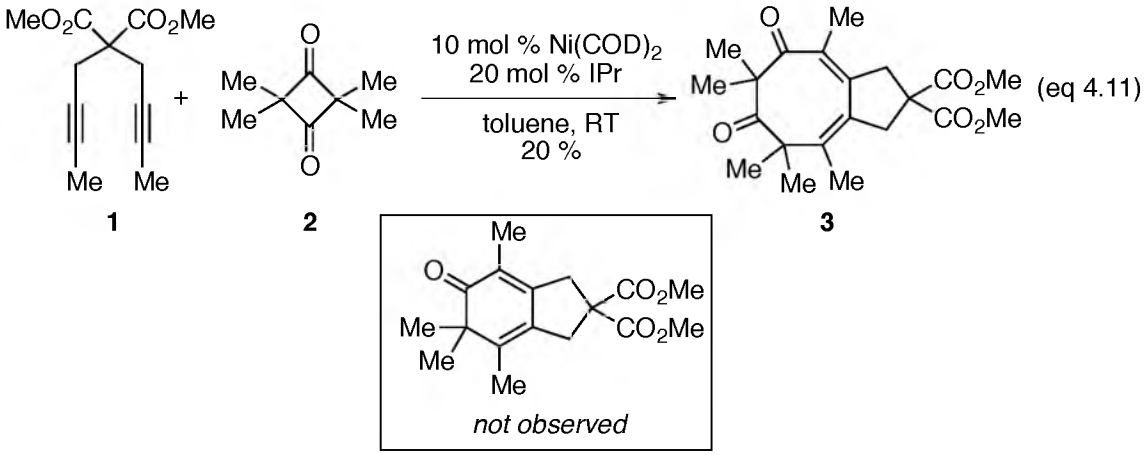


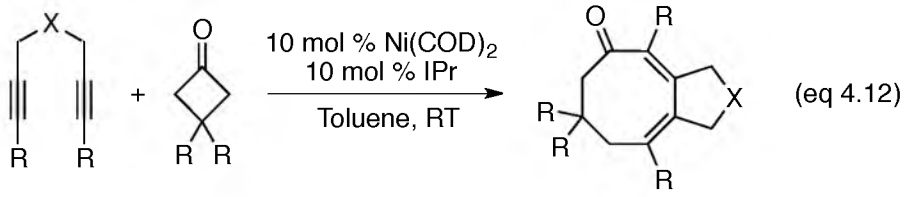
(eq 4.9)

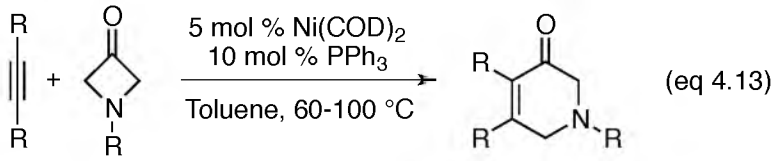
Recently, we reported the cycloaddition of diynes and ketene using a Ni-phosphine catalyst (eq 4.10).[8] Due to the difficulties in preparation and handling of ketenes, we became interested in investigating the ketene dimers as ketene surrogates. Interestingly, the Ni/IPr catalyst in presence of dimethyl ketene dimer **2** and diyne **1** afforded an eight-membered carbocycle **3** instead of a cyclohexadienone (eq 4.11).[9] These findings were consistent with the original report by Murakami's group in 2005, which describes the coupling of diynes and cyclobutanones (eq 4.12).[10] Since then, no progress has been made to explore other avenues by using this concept of C-C bond activation.[10] Recently, our research group and those of others independently discovered a Ni/PPh_3-catalyzed method for coupling azetidinones and alkynes to afford 3-piperidones; this method involves cleavage of the C-C bond attached to the carbonyl of the azetidinone (eq 4.13).[11] We surmised that if two tethered alkynes were employed instead of one, insertion of both of the alkynes into the azetidinone $C(sp^2)$-$C(sp^3)$ bond could occur, thus resulting in the formation of eight-membered nitrogen containing heterocyclic products (eq 4.14). Medium-sized heterocycles are prevalent among bioactive molecules.[12] Unfortunately, the synthesis of eight-membered rings poses a serious challenge because of enthalpic and entropic factors.[13-15]

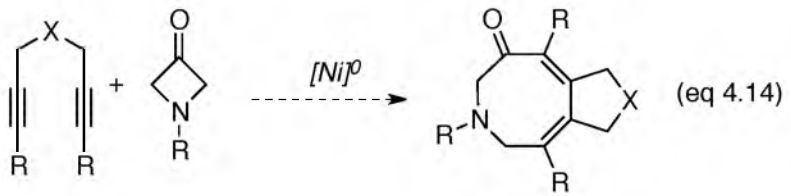


(eq 4.10)



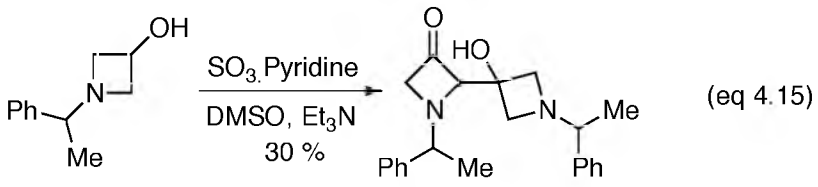






In contrast to cyclobutanone, which was used by the research group of Murakami, heteroatom-substituted cyclobutanones are prone to polymerization and decomposition.[16] Furthermore, self-condensation of heteroatom-substituted cyclobutanones occurs under

neutral as well as basic reaction conditions (eq 4.15).[16] Despite these challenges, we successfully developed a Ni/IPr catalyst that can effect the coupling of diynes and azetidinones to afford dihydroazocines in excellent yield.[17] This catalytic method not only provides medium-sized eight-membered heterocycles that are normally challenging to prepare but also represents a model system for the cleavage of $C(sp^2)$-$C(sp^3)$ bonds at low temperature.

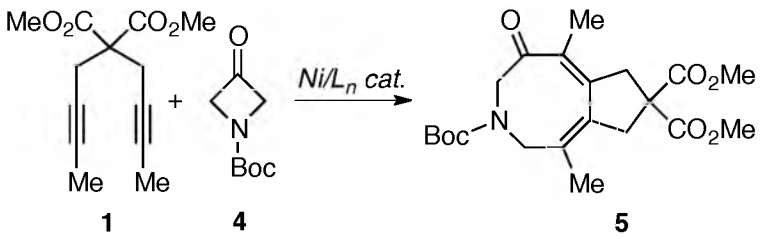


(eq 4.15)

Results and discussion

At the outset, we reasoned that self-condensation of the azetidinone could be minimized through the use of suitable protecting groups on the nitrogen atom of 3-azetidinones. The reaction between commercially available 3-Boc-protected azetidinone (**4**) and malonate diyne **1** was chosen as a model reaction (eq 4.16). The reaction optimization and substrate scope was studied in collaboration with Dr. Kainan Zhang. Given our success in using catalytic amounts of Ni/PPh_3 in toluene as reaction conditions for the coupling of azetidinones and alkynes, we initially evaluated these reactions conditions for the reaction between **1** and **4**. In the event, although moderate conversion of azetidinone **4** was observed, no desired product was detected (Table 4.1, entry 1). Other phosphine ligands were also evaluated (Table 4.1, entries 2–8), but these reactions also led to little or no desired product. Notably, the reactions where some desired product was formed were those in which electron-donating phosphines were used ($P(n\text{Bu})_3$, PCy_3,

and $P(Cyp)_3$; Table 4.1, entries 5-7, respectively). A side reaction that plagues many cycloaddition reactions is the oligomerization of alkyne units to give aromatic products.[18] We feared that this reaction was the cause of the low yields and therefore, we conducted the reaction using Ni/PCy_3 as the catalyst and employing slow addition of the diyne (Table 4.1, entry 6). Unfortunately, a low yield of product **5** was still obtained. We then turned our attention to the highly σ-donating N-heterocyclic carbene (NHC) ligand, IPr, owing to our previous success in using Ni/IPr in the cycloaddition of both diyne and enynes with carbonyl compounds such as aldehydes and ketones. Murakami and co-workers also used a Ni/IPr catalyst to facilitate the cycloaddition of diynes and cyclobutanones.[19] Ultimately, the use of IPr proved to be advantageous and the product **5** was obtained in 70 % yield when the reaction was conducted at room temperature (Table 4.1, entry 9).

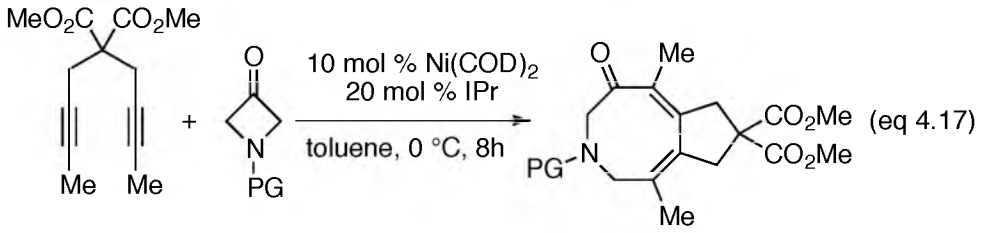


1 **4** **5** (eq 4.16)

We surmised that the C-C bond cleavage might be slow because the slow addition of the diyne did not lead to improved yields (see above). To facilitate this step, we conducted the reaction at higher temperatures (Table 4.2). Unfortunately, higher reaction temperatures proved to be deleterious to the coupling reaction and resulted in increased alkyne oligomerization. Specifically, the reaction performed at 60 °C and at 100 °C afforded the dihydroazocine product in 35 % and 21 % yield, respectively (Table 4.2, entries 2 and 3). These results suggested that lowering rather than increasing the reaction

temperature might result in higher product yield. Indeed, the yield of **5** improved significantly when the reaction temperature was lowered to 0 °C (Table 4.2, entry 4).[20] The use of a more dilute reaction mixture led to further improvement of the yield (Table 4.2, entries 4-6). Because previous C-C bond cleavage reactions were facilitated when they were conducted at higher temperatures, the results herein are unique in that the C-C bond cleavage step proceeds at 0 °C.[21]

Other protecting groups on the nitrogen atom of the 3-azetidinone were also evaluated (eq 4.17). The use of the methoxycarbonyl-protecting group **6** resulted in a lower yield than the use of Boc-protected azetidinone **4**. The use of the tosyl (Ts)-protecting group afforded the product in poor yield (**9**). However, the use of the benzhydryl (Bnh)-protecting group (**10**) led to an excellent yield (92 %) of the corresponding dihydroazocine **11**.

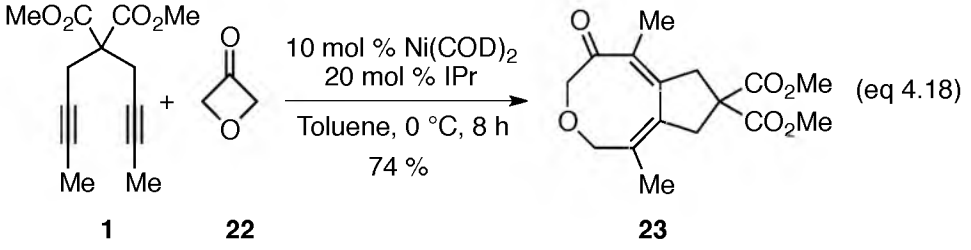


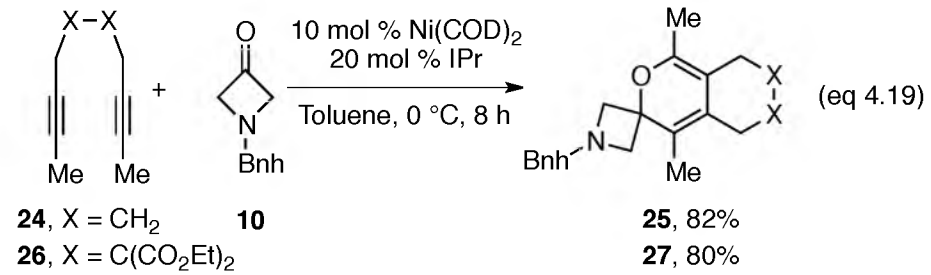
1

4 PG = Boc — **5**, 88%
6 PG = CO_2Me — **7**, 69%
8 PG = Ts — **9**, 25%
10 PG = Bnh (Benzhydryl) — **11**, ***92%***

The substrate scope of this reaction was investigated with various diynes (Scheme 4.1). The presence of a dioxolone moiety in the diyne was well tolerated under the reaction conditions and the dihydroazocine product **12** was obtained in good yield. Unsurprisingly, the presence of ether functional groups was tolerated (Scheme 4.1; **13** and **14**).[22] Notably, the sulfonamide-based diyne, which is not always well tolerated in

Ni-catalyzed cycloaddition reactions, reacted with azetidinone to provide the pyrrolidinyl-fused dihydroazocine product **15** in excellent yield.[23] The reaction of a diyne containing a sulfonyl group (**16**) afforded product in slightly lower yield than an ester-containing diyne (**5**). The ketone and nitrile functional groups did not interfere with the coupling reaction involving the azetidinone and diyne (**17** and **18**, Scheme 4.1). The success of the reaction is not dependent on the presence of the Thorpe–Ingold effect because the use of a diyne with an unsubstituted backbone afforded the corresponding dihydroazocine (**19**) in good yield. Because ester-containing compounds often cannot be used as therapeutics, we evaluated other substrates. Inspired by the recent work of Carriera and coworkers, oxetanyl and azetidinyl diynes were prepared and subjected to the optimized reaction conditions; the corresponding dihydroazocine products (**20** and **21**, Scheme 4.1), which contain a spirocyclic backbone, were obtained in good yield.[24] The Ni/IPr catalyst also efficiently coupled the 3-oxacyclobutanone (**22**) and diyne **1** under the standard reaction conditions, thus giving dihydrooxocine **23** in good yield (eq 4.18). Interestingly, when diynes **24** and **26**, which were expected to afford six-membered-ring-fused dihydroazocine products, were evaluated, the expected products arising from $C(sp^2)$-$C(sp^3)$ bond cleavage were not obtained. Instead, spirocyclic pyran products were formed in good yields (**25** and **27**, eq 4.19).

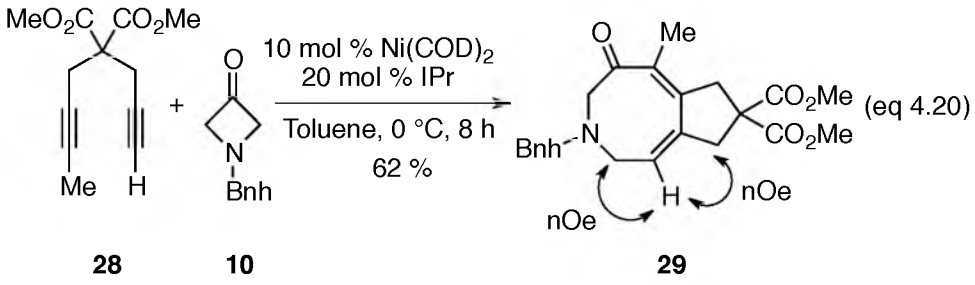




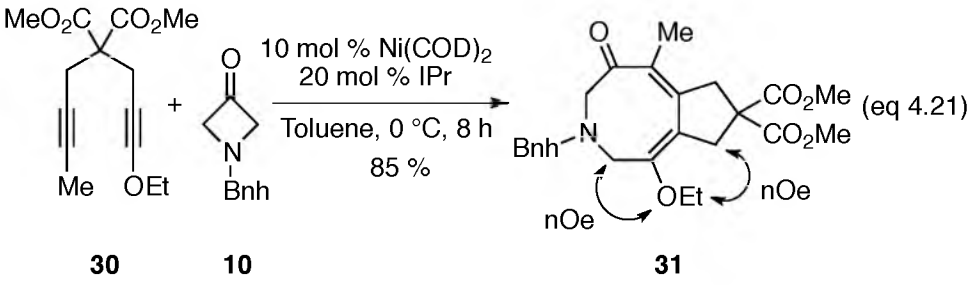
24, X = CH_2 **10** **25**, 82%

26, X = $C(CO_2Et)_2$ **27**, 80%

To address the question of regioselectivity when using an unsymmetrical diyne, diyne **28**, which contains a terminal alkyne and a methyl-substituted alkyne, was subjected to the optimized reaction conditions; only one regioisomer was observed (**29**; eq 4.20). Another unsymmetrical diyne, **30**, the termini of which differ electronically rather than sterically, was also evaluated; again, only one regioisomer was observed (**31**, eq 4.21).



28 **10** **29**



30 **10** **31**

Mechanism

A proposed mechanism for the cycloaddition reaction is shown in Scheme 4.2. Typically, such a cycloaddition would begin with oxidative coupling between an alkyne

and the carbonyl group.[25,26] In this case, oxidative coupling would afford a spirocyclic intermediate **M_1**. Subsequent insertion of the pendant alkyne would give the intermediate **M_2**, which could then undergo either reductive elimination (to afford products such as **25** and **27**) or β-carbon elimination to afford metallacycle **M_3**. Finally, C-C bond forming reductive elimination occurs to give the dihydroazocine product and the catalyst.

In the cycloaddition of unsymmetrical diyne **28**, the regioselectivity is governed by the difference in the size of the substituents on the alkynes. That is, oxidative coupling between the alkyne bearing the larger group occurs first to minimize steric interactions between the group and the ligand. Indeed, this type of regioselectivity has been found in various cycloaddition reactions catalyzed by nickel complexes. However, in the cycloaddition of unsymmetrical diyne **30**, the electronic nature of the alkyne, rather than steric factors, dictate the observed regioselectivity. That is, the oxidative coupling of the alkyne bearing the methyl group (A = Me) is more favored than the coupling of the alkyne with perturbed electronics (B = OEt). This type of electronically driven regioselectivity has not been exploited extensively in cycloaddition reactions.[27]

Conclusion

In conclusion, we have demonstrated that eight-membered heterocycles can be easily accessed through Ni/IPr-catalyzed coupling of 3-azetidinone (or 3-oxetanone) and diynes. The decomposition of these constrained heterocycles could be avoided by using specific reaction conditions. This method involves an interesting C-C bond cleavage step, which operates smoothly at 0 °C.

General experimental

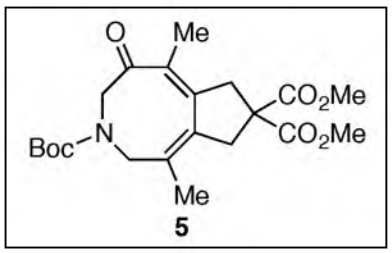
All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2-filled glove box unless otherwise noted. Toluene was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. $Ni(COD)_2$ was purchased from Strem and used without further purification. 3-Boc-azetidinone **4**, and 3-benzhydryl-azetidinone **10** were purchased from Sigma-Aldrich and Synthonix, respectively, and used as received. Diynes were prepared according to the reported procedures. All other reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. ^1H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 300, 400, 500, and 100, 125 MHz, respectively, unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^1H and to the central line of a triplet at 77.23 ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, t, q, and quint stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, quartet, and quintet, in that order. All ^{13}C NMR spectra were proton decoupled. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer.

General procedure for cycloaddition

In a glove box, the scintillation vial equipped with a magnetic stir bar was charged with diyne (1.2 equiv) and azetidinone (1 equiv, 0.05 M). To this mixture in toluene was added catalyst solution which was prepared in toluene by mixing $Ni(COD)_2$ and IPr in 1:2 molar ratio (the stock catalyst solution was allowed to stir for at least 6 h before use). The reaction was immediately brought outside of the glove box, sealed, and stirred at 0

°C for 8 h. The solvent was removed under vacuum and the product was purified by silica gel flash column chromatography.

(1Z,6Z)-3-Tert-butyl 8,8-dimethyl 1,6-dimethyl-5-oxo-4,5-dihydro-2Hcyclopenta[d]azocine-3,8,8(7H,9H)-tricarboxylate (**5**)

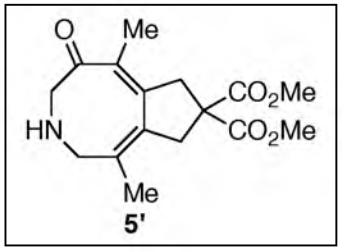


5

The general procedure for cycloaddition was used with diyne **1** (16.6 mg, 0.07 mmol), N-Boc azetidinone **4** (10 mg, 0.05 mmol). The crude product was purified by flash column chromatography on silica gel (50% diethyl ether in pentane or 30% EtOAc in hexanes) to afford the azocine **5** as pale yellow oil, in 88% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.00 (s, 2H), 3.87 (s, 2H), 3.76 (s, 6H), 3.17 (s, 2H), 3.14 (s, 2H), 1.94 (s, 3H), 1.92 (s, 3H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 171.6, 55.8, 53.4, 41.6, 39.1, 28.5, 16.4 (Please note that due to the presence of Boc-group, some peaks were missing in ^{13}CNMR acquired at about 20 °C. To address this issue, deprotection of Boc-group was performed which afforded **5** (for Boc deprotection procedure and full characterization of **5'**, see next entry). IR (CH_2Cl_2, cm^{-1}): 2977, 1735, 1695, 1435, 1368, 1251, 1205, 1159, 1070. HRMS (ESI+) calcd for $C_{21}H_{29}NO_7Na$ [M+Na]+ 430.1842, found 430.1847.

(1Z,6Z)-dimethyl 1,6-dimethyl-5-oxo-4,5,7,9-tetrahydro-2H-cyclopenta[d]azocine-8,8(3H)-dicarboxylate (**5'**)



5'

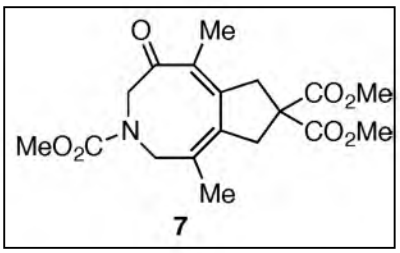
To a solution of **5** (8 mg, 0.01 mmol, 0.1 M) in DCM (0.18ml), trifluoroacetic acid was added (20.4 mg, 0.18 mmol, 0.013 ml). The reaction mixture was stirred at room

temperature for 5 h. The solvent was removed under vacuum. The residue was diluted by dichloromethane (1ml) and washed with saturated aqueous K_2CO_3 solution. The organic phase was dried by Na_2SO_4 and solvent was removed under vacuum to yield **5'** in 90% as an orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 3.89 (br, 2H), 3.77 (s, 6H), 3.71 (bs, 3H), 3.23 (s, 2H), 3.21 (s, 2H), 2.10 (s, 3H), 1.95 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 194.1, 171.3, 150.9, 142.9, 134.4, 131.9, 55.7, 53.6, 48.8, 48.2, 42.0, 39.4, 21.8, 16.2. IR (CH_2Cl_2, cm^{-1}): 2960, 1737, 1676, 1438, 1273, 1206. HRMS (ESI++) calcd for $C_{16}H_{22}NO_5$ [M]+ 308.1498, found 308.1500.

(1Z,6Z)-Trimethyl 1,6-dimethyl-5-oxo-4,5-dihydro-2H-cyclopenta [d]azocine-3,8,8(7H,9H)-tricarboxylate (7)

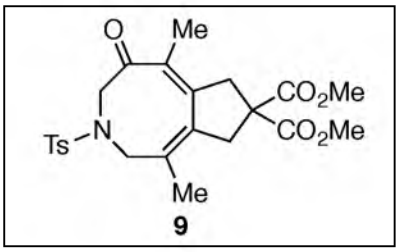
The general procedure for cycloaddition was used with diyne **1** (22.0 mg, 0.92 mmol), azetidinone **6** (9.1 mg, 0.07 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (60% diethyl ether in pentane) to afford the azocine **7** as light yellow oil, in 69% yield.



7

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 4.07–4.11 (br, 1H), 4.03–4.07 (br, 2H), 3.89–3.94 (br, 1H), 3.84–3.89 (br, 1H), 3.75 (s, 6H), 3.71 (s, 3H), 3.19 (s, 2H), 3.16 (s, 2H), 1.96 (s, 3H), 1.92 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ (ppm) 197.6, 171.7, 156.5, 149.2, 137.7, 134.5, 133.8, 55.9, 53.5, 53.4, 51.0, 49.4, 41.8, 39.1, 21.6, 16.3. IR (CH_2Cl_2, cm^{-1}): 2956, 1737, 1704, 1654, 1444, 1402, 1233, 1202, 1069. HRMS (ESI++) calcd for $C_{18}H_{23}NO_7$ [M+H]+ 366.1553, found 366.1546.

(1Z,6Z)-Dimethyl 1,6-dimethyl-5-oxo-3-tosyl-4,5,7,9-tetrahydro-2H-cyclopenta[d]azocine-8,8(3H)-dicarboxylate (**9**)

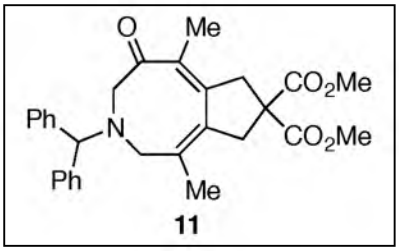


9

The general procedure for cycloaddition was used with diyne **1** (18.9 mg, 0.08 mmol), 3-azetidinone **8** (14.8 mg, 0.06 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (50% diethyl ether in pentane or 30% EtOAc in hexanes) to afford the azocine **9** as pale yellow oil, in 25% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.74 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 4.01 (s, 2H), 3.75 (s, 6H), 3.64 (s, 2H), 3.17 (s, 2H), 3.13 (s, 2H), 2.41 (s, 3H), 2.05 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ (ppm) 195.2, 171.6, 149.5, 143.8, 138.9, 136.2, 134.7, 133.8, 129.8, 128.2, 55.8, 53.6, 51.7, 50.3, 41.9, 39.1, 21.9, 21.2, 16.2. IR (CH_2Cl_2, cm^{-1}): 2955, 1735, 1652, 1436, 1349, 1257, 1159, 1087, 1027, 720. HRMS (ESI+) calcd for $C_{23}H_{27}NO_7NaS$ [M+Na]+ 484.1406, found 484.1407.

(1Z,6Z)-dimethyl 3-benzhydryl-1,6-dimethyl-5-oxo-4,5,7,9-tetrahydro-2HCyclopenta[d]azocine-8,8(3H)-dicarboxylate (**11**)



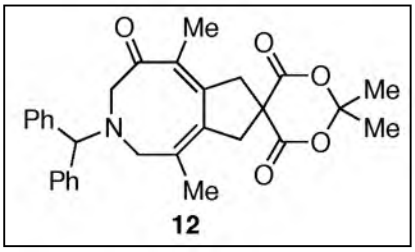
11

The general procedure for cycloaddition reaction was used with diyne **1** 27.8 mg, 0.11 mmol), azetidinone **10** (23.3 mg, 0.09 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (25% diethyl ether in pentane or 15% EtOAc in hexanes) to afford the azocine **11** as pale yellow solid in 92% yield. Mp: 50-52 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 (d, J = 7.2 Hz, 4H), 7.26–7.21 (t, J = 7.2 Hz,

4H), 7.12 (t, J = 7.4 Hz, 2H), 4.66 (s, 1H), 3.70 (s, 6H), 3.30–3.44 (br, 1H), 3.15 (s, 4H), 2.87 (s, 2H), 1.98 (d, 3H), 1.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.9, 171.8, 148.8, 143.7, 137.7, 137.5, 134.5, 128.9, 128.1, 127.3, 73.8, 56.3, 55.3, 54.4, 53.4, 41.9, 39.3, 22.0, 15.8. IR (CH_2Cl_2, cm^{-1}): 2954, 1734, 1635, 1559, 1453, 1435, 1264, 1204, 1069, 732, 704. HRMS (ESI+) calcd for $C_{29}H_{32}NO_5$ [M+H]+ 474.2280, found 474.2287.

(1Z,6Z)-tert-butyl 1,2',2',6-tetramethyl-4',5,6'-trioxo-4,5,7,9-tetrahydrospiro[cyclopenta[d]azocine-8,5'-[1,3]dioxane]-3(2H)-carboxylate (**12**)



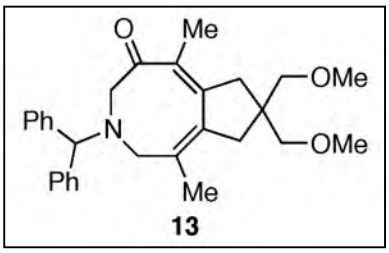
12

The general procedure was used with diyne (24.1 mg, 0.09 mmol), azetidinone **10** (19.2 mg, 0.08 mmol). The crude reaction mixture was purified by flash column chromatographyon silica gel (60% diethyl ether in pentane or 30% EtOAc in hexanes) to afford the azocine **12** as a slightly yellow solid in 78% yield. Mp: 148–150 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 (d, *J* = 7.2 Hz, 4H), 7.28 (t, *J* = 7.2 Hz, 4H), 7.17 (t, *J* = 7.2 Hz, 2H), 4.72 (s, 1H), 3.48 (br, 2H), 3.26 (s, 2H), 3.23 (s, 2H), 2.99 (s, 2H), 2.01 (s, 3H), 1.89 (s, 3H), 1.81 (s, 3H), 1.79 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.7, 170.4, 147.6, 143.5, 138.0, 136.4, 134.2, 128.8, 128.0, 127.2, 105.4, 73.7, 55.4, 54.2, 49.6, 45.3, 43.5, 29.2, 29.1, 22.1, 15.8. IR (CH_2Cl_2, cm^{-1}): 2924, 1775, 1742, 1641, 1453, 1391, 1301, 1206, 1045. HRMS (ESI+) calcd for $C_{30}H_{32}NO_5$ [M+H]+ 486.2280, found 486.2281.

(1Z,6Z)-3-Benzhydryl-8,8-bis((benzyloxy)methyl)-1,6-dimethyl-3,4,8,9-

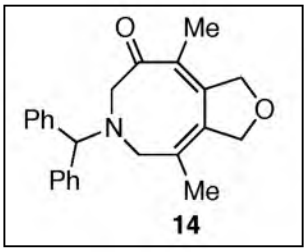
tetrahydro-2Hcyclopenta[d]azocin-5(7H)-one (**13**)



13

The general procedure was used with diyne (12.6 mg, 0.06 mmol), azetidinone **10** (12.0 mg, 0.05 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (30% diethyl ether in pentane) to afford the azocine **13** as a pale yellow oil in 48% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.51 (d, 4H), 7.26 (t, 4H), 7.14 (t, 2H), 4.69 (s, 1H), 3.32 (s, 7H), 3.23 (s, 5H), 2.91 (s, 2H), 2.47 (s, 2H), 2.45 (s, 2H), 1.98 (s, 3H), 1.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 203.0, 152.5, 143.9, 140.3, 134.4, 128.9, 128.2, 127.3, 76.2, 73.8, 59.7, 43.7, 40.8, 37.6, 22.1, 15.8. IR (CH_2Cl_2, cm^{-1}): 2924, 2886, 2824, 1727, 1635, 1586, 1453, 1375, 1336, 1304, 1282, 1111, 1043. HRMS (ESI+) calcd for $C_{29}H_{36}NO_3$ [M+H]+ 466.2690, found 446.2687.

(3aE,9E)-6-Benzhydryl-4,9-dimethyl-3,5,6,7-tetrahydrofuro[3,4-d] azocin-8(1H)-one (**14**)



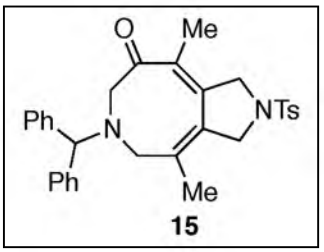
14

The general procedure was used with diyne (12.4 mg, 0.10 mmol), azetidinone **10** (20.1 mg, 0.08 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (30% diethyl ether in pentane or 15% EtOAc in hexanes) to afford the azocine **14** as a yellow solid in 91% yield. Mp: 124-126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.51 (d, J = 7.6 Hz, 4H), 7.28 (t, J = 7.2 Hz, 4H), 7.17 (t, J = 7.2 Hz, 2H), 4.75 (s, 1H), 4.65 (s, 2H), 4.60 (s, 2H), 3.45 (s, 2H), 2.99 (s, 2H), 1.97 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 203.7, 147.4, 143.4, 137.1, 136.7, 131.8, 128.8, 128.0, 127.3, 73.8, 73.2, 71.9, 55.5, 54.5, 22.1, 15.1. IR

(CH_2Cl_2, cm^{-1}): 2843, 1644, 1601, 1492, 1453, 1049. HRMS (ESI+) calcd for $C_{24}H_{25}NO_2Na$ [M+Na]+382.1783, found 382.1796.

The crystals suitable for single crystal X-ray crystallography were grown from slow diffusion of hexanes into a saturated solution of **14** in tetrahydrofuran.

(3aE,9E)-6-Benzhydryl-4,9-dimethyl-2-tosyl-2,3,6,7-tetrahydro-1H-pyrrolo[3,4-d]azocin-8(5H)-one (**15**)



15

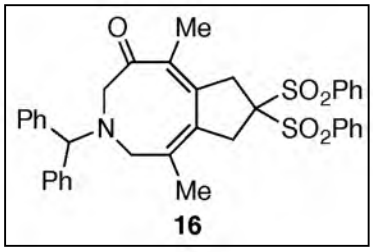
The general procedure was used with diyne (26.6 mg, 0.09 mmol), azetidinone **10** (19.1 mg, 0.08 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (30% diethyl ether in pentane or 15-20% EtOAc in hexanes) to afford the azocine **15** as a yellow solid in 79% yield. Mp: 122–124 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.73 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 7.5 Hz, 2H), 7.31 (d, J = 9 Hz, 2H), 7.27 (t, J = 7.5 Hz, 4H), 7.16 (t, J = 7.0 Hz, 2H), 4.66 (s, 1H), 4.15 (s, 2H), 4.11 (s, 2H), 3.24–3.31 (br, 2H), 2.83 (s, 2H), 2.37 (s, 3H), 1.95 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.9, 144.3, 144.1, 143.2, 138.7, 134.1, 133.8, 133.3, 130.1, 128.9, 127.9, 127.3, 73.7, 55.0, 54.2, 53.8, 52.0, 22.2, 21.7, 15.5. IR (CH_2Cl_2, cm^{-1}): 3029, 2925, 2853, 1644, 1597, 1452, 1347, 1163, 1095, 1044. HRMS (ESI+) calcd for $C_{31}H_{32}N_2O_3SNa$ [M+Na]+ 535.2031, found 535.2044.

1Z,6Z)-3-Benzhydryl-1,6-dimethyl-8,8-bis(phenylsulfonyl)-3,4,8,9-tetrahydro-2Hcyclopenta[d]azocin-5(7H)-one (**16**)

The general procedure was used with diyne (36.6 mg, 0.09 mmol), azetidinone **10** (18.1 mg, 0.07 mmol). The crude reaction mixture was purified by flash column

chromatography on silica gel (50% diethyl ether in pentane or 30% EtOAc in hexanes) to afford the azocine **16** as a yellow solid in 59%. Mp = 192 °C (Decomp).

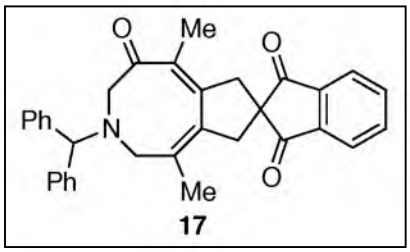


16

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.99 (d, *J* = 7.2 Hz, 4H), 7.65 (t, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 8 Hz, 4H), 7.46 (d, *J* = 7.2 Hz, 4H), 7.27 (t, *J* = 7.2 Hz, 4H), 7.17 (t, *J* = 7.2 Hz, 2H), 4.58 (s, 1H), 3.56 (s, 2H), 3.47 (s, 2H), 3.09 (br, 2H), 2.70 (s, 2H), 1.95 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.1, 146.2, 143.2, 139.5, 136.7, 135.4, 135.2, 134.4, 131.1, 129.2, 128.9, 127.9, 127.3, 88.9, 73.6, 55.2, 54.0, 39.4, 36.6, 22.4, 16.2. IR (CH_2Cl_2, cm^{-1}): 3062, 2925, 2852, 1641, 1585, 1449, 1333, 1150, 1079, 1044. HRMS (ESI+) calcd for $C_{37}H_{36}NO_5S_2$ [M+Na]+ 638.2035, found 638.2033.

(1Z,6Z)-3-Benzhydryl-1,6-dimethyl-3,4-dihydrospiro[cyclopenta [d]azocine-8,2'-indene]-1',3',5(2H,7H,9H)-trione (**17**)

The general procedure was used with diyne (37.8 mg, 0.15 mmol), azetidinone **10** (29.9 mg, 0.13 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (30% EtOAc in hexanes) to afford the azocine **17** as pale yellow oil in 88% yield.

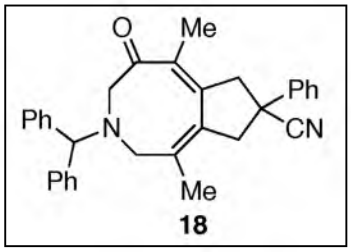


17

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.99 (m, 2H), 7.86 (m, 2H), 7.53 (d, *J* = 8 Hz, 4H), 7.28 (t, *J* = 7.5 Hz, 4H), 7.16 (t, *J* = 7.0 Hz, 2H), 4.74 (s, 1H), 3.52 (br, s, 2H), 3.02 (s, 2H), 2.92 (s, 2H), 2.90 (s 2H), 1.99 (s, 3H), 1.87 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.8 202.6, 149.6, 143.5 141.4, 138.0, 137.3, 136.2, 134.0, 128.7, 127.9, 127.1, 123.8, 73.6, 55.5, 55.3, 54.2, 41.0 39.2 22.0, 15.8. IR (CH_2Cl_2, cm^{-1}): 3060, 3029, 2926,

2847, 1744, 1706, 1637, 1595, 1492, 1452, 1373, 1332, 1306, 1272, 1042, 920, 734, 705. HRMS (ESI+) calcd for $C_{33}H_{29}NO_3Na$ [M+Na]+ 510.2045, found 510.2048.

(1Z,6Z)-3-benzhydryl-1,6-dimethyl-5-oxo-8-phenyl-3,4,5,7,8,9-hexahydro-2Hcyclopenta[d]azocine-8-carbonitrile (**18**)

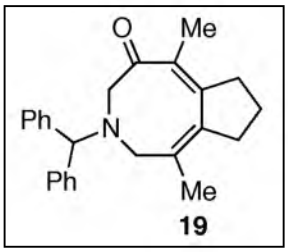


18

The general procedure was used with diyne (19.7 mg, 0.08 mmol), azetidinone **10** (17.6 mg, 0.07 mmol). The crude reaction mixture was purified by flash column chromatography on silica gel (15% EtOAc in hexanes) to afford the azocine **18** as pale yellow oil in 64% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (t, *J* = 6.5 Hz, 4H), 7.46 (d, *J* = 7.1 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.36 (d, *J* = 6.7 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 4H), 7.18 (t, *J* = 7.4 Hz, 2H), 4.75 (s, 1H), 3.62-3.49 (br, 2H), 3.46 (d, *J* = 4.6 Hz, 1H), 3.42 (d, *J* = 6.7 Hz, 1H), 3.13 (d, *J* = 6.6 Hz, 1H), 3.09 (d, *J* = 4.6 Hz, 1H), 3.02 (s, 2H), 2.06 (s, 3H), 1.92 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 203.1, 147.3, 143.6, 143.5, 139.2, 136.9, 135.3, 129.0, 128.1, 127.5, 127.4, 126.0, 123.7, 73.9, 55.3, 54.5, 47.9, 45.4, 43.8, 22.3, 16.1. IR (CH_2Cl_2, cm^{-1}): 3060, 3027, 2933, 2869, 1661, 1491, 1451, 1375, 1315, 1276, 1205, 1177, 1074, 1026, 941, 742, 702, 639. HRMS (ESI+) calcd for $C_{32}H_{31}N_2O$ [M+H]+ 510.2045, found 510.2048.

(1Z,6Z)-3-Benzhydryl-1,6-dimethyl-3,4,8,9-tetrahydro-2H-cyclopenta [d]azocin-5(7H)-one (**19**)



19

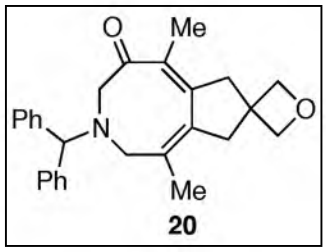
The general procedure for cycloaddition was used with diyne (12.2 mg, 0.101 mmol, azetidinone **10** (20 mg, 0.0843). The crude reaction mixture was purified by flash column

chromatography on silica gel (10% diethyl ether in pentane or 5% EtOAc in hexanes) to afford the eight-membered ring product **19** as pale yellow oil in 68% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.53 (d, J = 7.2 Hz, 4H), 7.28 (t, J = 7.2 Hz, 4H), 7.16 (t, J = 7.2 Hz, 2H), 4.71 (s, 1H), 3.29–3.57 (br, 2H), 2.92 (s, 2H), 2.57 (t, J = 7.6 Hz, 4H), 2.02 (s, 3H), 1.90 (s, 3H), 1.77 (p, J = 7.6Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 203.1, 154.0, 143.8, 141.9, 135.5, 133.5, 128.7, 128.0, 127.1, 73.7, 53.4, 54.3, 35.1, 31.9, 22.1, 22.0, 15.8. IR (CH_2Cl_2, cm^{-1}): 2930, 1704, 1660, 1451, 1378, 1317, 1279. HRMS (ESI+) calcd for $C_{25}H_{28}NO$ [M+H]+ 358.2171, found 358.2172.

(1Z,6Z)-3-Benzhydryl-1,6-dimethyl-3,4,7,9-tetrahydrospiro[cyclopenta [d]azocine-8,3'-oxetan]-5(2H)-one (**20**)

The general procedure for cycloaddition was used with diyne (25.8 mg, 0.14 mmol, azetidinone **10** (34.3 mg, 0.16). The crude reaction mixture was purified by flash column chromatography on silica gel (30% EtOAc in hexanes) to afford the eight-membered ring product **20** as pale yellow oil in 87% yield.

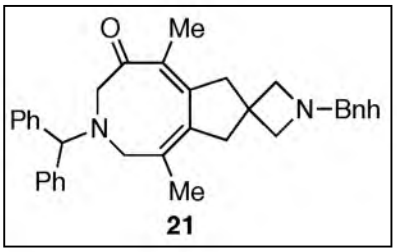


20

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.51 (d, J = 7.6 Hz, 4H), 7.27 (t, J = 8 Hz, 4H), 7.15 (t, J = 7.6 Hz, 2H), 4.70 (s, 1H), 4.56 (m, 4H), 3.39 (br, s, 2H), 2.89 (m, 6H), 2.04 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.8, 150.6, 143.5, 139.2, 136.8, 134.3, 128.7, 127.9, 127.1, 83.1, 73.6, 55.0, 54.3, 45.7 42.9, 42.6, 21.9, 15.7. IR (CH_2Cl_2, cm^{-1}): 3059, 3027, 2924, 2860, 1634, 1588, 1490, 1449, 1372, 1333, 1281, 1042, 978, 924, 834, 748, 705, 670. HRMS (ESI+) calcd for $C_{27}H_{29}NO_2Na$ [M+Na]+ 422.2096, found 422.2109.

(1'Z,6'Z)-1,3'-dibenzhydryl-1',6'-dimethyl-3',4',7',9'-tetrahydrospiro

[azetidine-3,8'-cyclopenta[d]azocin]-5'(2'H)-one (**21**)

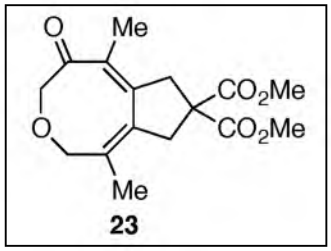


21

The general procedure for cycloaddition was used with diyne (30.9 mg, 0.09 mmol, azetidinone **10** (18.7 mg, 0.08). The crude reaction mixture was purified by flash column chromatography on silica gel (10-30% EtOAc in hexanes) to afford the eight-membered ring product **21** as pale yellow oil in 71% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.51 (d, J = 7.6 Hz, 4H), 7.41 (d, J = 8 Hz, 4H), 7.26 (t, J = 8 Hz, 7.2 Hz, 2H), 7.16 (m, 4H), 4.69 (s, 1H), 4.34 (s, 1H), 3.40 (br, s, 2H), 3.05 (m, 4H) 2.87 (s, 2H), 2.79 (s, 2H), 2.78 (s, 2H), 2.01 (s, 3H), 1.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 202.9, 152.0, 143.6, 142.4, 140.2, 136.2, 133.9 128.7, 128.5, 127.9, 127.7, 127.2, 127.0, 78.3, 73.6, 65.3, 55.0, 54.3, 47.0 43.8, 37.3 22.0, 15.7. IR (CH_2Cl_2, cm^{-1}): 3060, 3027, 2925, 2818, 1635, 1590, 1492, 1452, 1337, 1305, 1278, 1248, 1072, 1030, 922, 744, 703. HRMS (ESI+) calcd for $C_{40}H_{41}N_2O$ [M+H]+ 565.3219, found 565.3218.

(1Z,6Z)-Dimethyl 1,6-dimethyl-5-oxo-4,5,7,9-tetrahydrocyclopenta [d]oxocine-8,8(2H)-dicarboxylate (**23**)



23

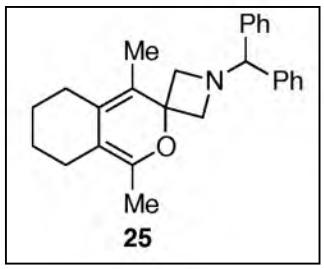
The general procedure was used with diyne **1** (78.7 mg, 0.33 mmol), oxetanone **22** (20.0 mg, 0.27 mmol). The crude product was purified by flash column chromatography on silica gel (50% Et_2O in hexanes) to afford the oxocine **23** as slightly pale yellow oil in 74% yield.

^{1}H NMR (400 MHz, C_6D_6): δ (ppm) 3.99 (s, 2H), 3.98 (s, 2H), 3.73 (s, 6H), 3.19 (s, 2H),

3.17 (s, 2H), 1.99 (s, 3H), 1.90 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ (ppm) 199.2, 171.4, 149.5, 140.0, 134.8, 134.5, 69.7, 68.5, 55.7, 53.2, 41.5, 38.8, 21.2, 15.7. IR (CH_2Cl_2, cm^{-1}): 2956, 2868, 2939, 2872, 1735, 1661, 1601, 1449, 1368, 1287, 1205, 1096, 1050, 1034, 920 864, 737, 704. HRMS (ESI+) calcd for $C_{16}H_{20}O_6Na$ [M+Na]+ 331.1158, found 331.1167.

1-Benzhydryl-1',4'-dimethyl-5',6',7',8'-tetrahydrospiro [azetidine-3,3'-isochromene] (**25**)

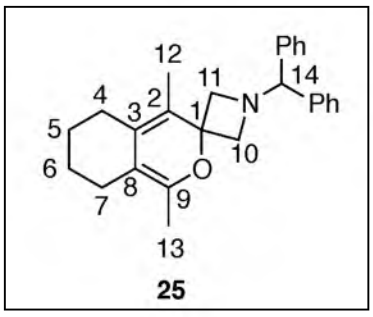
The general procedure was used with diyne **24** (14.9 mg, 0.11 mmol), azetidinone **10** (22.0 mg, 0.09 mmol). The crude product was purified by flash column chromatography on florisil (30% diethyl ether in pentane) to afford the azocine **25** as colorless oil in 82% yield.



25

^{1}H NMR (500 MHz, C_6D_6): δ (ppm) 7.44 (dd, *J* = 8.1, 1.0 Hz, 4H), 7.12 (t, *J* = 7.6 Hz, 4H), 7.01 (t, *J* = 7.4 Hz, 2H), 4.33 (s, 1H), 3.59 (dd, *J* = 6.9, 1.9 Hz, 2H), 3.31 (dd, *J* = 6.9, 1.8 Hz, 2H), 2.15 (t, *J* = 4.9 Hz, 2H), 2.06 (t, *J* = 5.0 Hz, 2H), 2.03 (s, 3H), 1.76 (s, 3H), 1.46 – 1.38 (m, 4H). ^{13}C NMR (125 MHz, C_6D_6): δ (ppm) 143.9, 143.5, 129.0, 128.9, 128.2, 127.6, 126.8, 120.0, 109.1, 79.0, 75.2, 66.5, 26.9, 25.8, 24.8, 24.5, 16.6, 13.1. IR (CH_2Cl_2, cm^{-1}): 3027, 2932, 2855, 1659, 1599, 1491, 1451, 1207, 1076, 1029, 743, 702. HRMS (ESI+) calcd for $C_{26}H_{30}NO$ [M+H]+ 372.2327, found 372.2330.

g-HMBC summary: The following cross peaks were observed: H(4) and C(5); H(5) and C(6); H(6) and C(5); H(7) and C(6); H(10) and C(1); C(1); H(11); H(10) and C(11); H(10) and C(14); H(11) and C(1); H(11) and

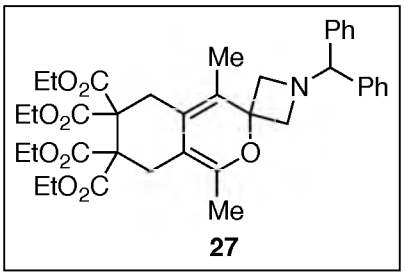


25

C(10); H(11) and C(14); H(12) and C(2); H(12) and C(3); H(13) and C(8).

Tetraethyl 1-benzhydryl-1',4'-dimethylspiro[azetidine-3,3'-isochromene]-6',6',7',7'(5'H,8'H)-tetracarboxylate (**27**)

The general procedure was used with diyne **26** (41.2 mg, 0.09 mmol), azetidinone **10** (19.3 mg, 0.08 mmol). The crude product was purified by flash column chromatography on silica gel (10-30% EtOAc in hexanes) to afford the azocine **27** as colorless oil in 80% yield.

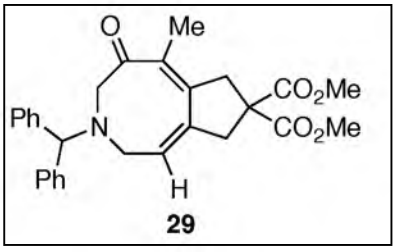


27

^{1}H NMR (400 MHz, C_6D_6): δ (ppm) 7.41 (d, J = 7.6 Hz, 4H), 7.24 (t, *J* = 7.2 Hz, 4H), 7.15 (t, J = 7.2 Hz, 2H), 4.37 (s 1H), 4.17 (m, 8H), 3.42 (d, J = 8.4 Hz, 2H), 3.14 (d, J = 8.4 Hz, 2H), 2.94 (s, 2H), 2.90 (s, 2H), 2.05 (s, 3H), 1.80 (s, 3H), 1.24 (m, 12H). ^{13}C NMR (100 MHz, C_6D_6): δ (ppm) 170.1 169.9 144.6, 142.6, 128.5, 127.5 127.2, 122.8, 120.5, 105.5, 78.3, 74.9, 65.3, 61.88, 61.81, 58.5, 57.8, 31.3, 30.1 16.3, 14.0, 12.9. IR (CH_2Cl_2, cm^{-1}): 3061, 2984, 2939, 2872, 1735, 1661, 1601, 1449, 1368, 1287 1205, 1096, 1050, 1034 920 864, 737, 704. HRMS (ESI+) calcd for $C_{38}H_{46}NO_9$ [M+H]+ 660.3173, found 660.3167.

(1Z,6Z)-Dimethyl 3-benzhydryl-6-methyl-5-oxo-4,5,7,9-tetrahydro-2Hcyclopenta[d]azocine-8,8(3H)-dicarboxylate (**29**)

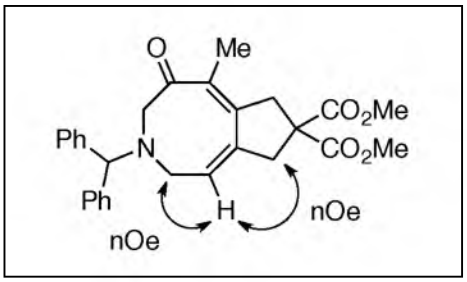
The general procedure was used with diyne **28** (17.8 mg, 0.08 mmol), azetidinone **10** (15.8 mg, 0.06 mmol). The crude product was purified by flash column chromatography on silica gel (15% EtOAc in hexanes)



29

to afford the azocine **29** as pale yellow oil in 62% yield.

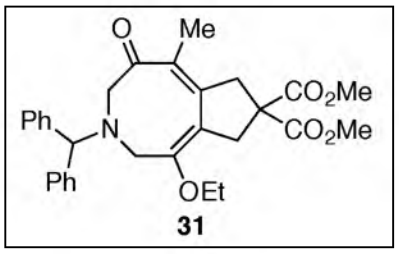
^{1}H NMR (400 MHz, C_6D_6): δ (ppm) 7.53 (d, J = 8.0 Hz, 4H), 7.30 (t, J = 7.6 Hz, 4H), 7.19 (t, J = 8.0 Hz, 2H) 6.08 (t, J = 8.0 Hz, 1H), 4.70 (s, 1H), 3.77 (s, 6H), 3.41 (br, s, 2H), 3.24 (s, 2H), 3.23 (s, 2H), 2.94 (d, J = 8.4 Hz, 2H), 1.93 (s, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ (ppm) 203.1, 171.4, 146.3, 144.1, 143.2, 135.5, 128.8, 128.0, 127.2, 126.6, 73.6, 56.1, 55.0, 53.3, 48.4, 43.0, 41.4, 15.8. IR (CH_2Cl_2, cm^{-1}): 3060, 3029, 2954, 2852, 1735, 1657, 1599, 1494, 1450, 1267, 1202, 1170, 1074, 734,704. HRMS (ESI+) calcd for $C_{28}H_{30}NO_5$ [M+H]+ 460.2124, found 460.2126.



The regiochemistry was assigned by 1d-NOESY experiment. The correlation of vinylic 'H' with two methylenes was observed.

(3aZ,9E)-6-Benzhydryl-4-ethoxy-9-methyl-3,5,6,7-tetrahydrofuro [3,4-d]azocin-8(1H)-one (**31**)

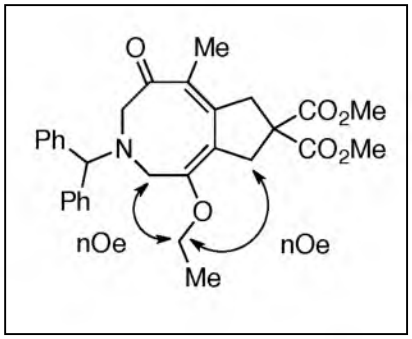
The general procedure was used with diyne **30** (13.1 mg, 0.08 mmol), azetidinone **10** (17.1 mg, 0.07 mmol). The crude product was purified by flash column chromatography on silica gel (10-15% EtOAc in hexanes) to afford the azocine **31** as pale yellow oil in 85% yield.



31

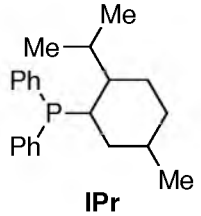
^{1}H NMR (300 MHz, C_6D_6): δ (ppm) 7.53 (d, J = 7.2 Hz, 4H), 7.26 (m, 4H), 7.20 (m, 2H), 4.76 (s, 1H), 4.72 (s, 2H), 4.61 (s, 2H), 3.85 (q, J = 6.9 Hz, 2H), 3.55 (br, s, 2H), 3.06 (br, s, 2H), 1.80 (s, 3H), 1.24 (t, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ (ppm) 202.3, 154.3, 149.6, 142.8, 128.8, 128.0, 127.5, 121.8, 95.0, 74.0, 73.6, 71.1, 64.8 55.0, 49.2,

15.6, 15.0. IR (CH_2Cl_2, cm^{-1}): 3061, 3029, 2980 2931, 2853, 1723, 1654, 1632, 1587, 1492, 1452, 1376, 1347, 1277, 1208, 1145, 1109, 1031, 924, 761, 748, 705. HRMS (ESI+) calcd for $C_{25}H_{27}NO_3Na$ [M+Na]+ 412.1889, found 412.1895.



The regiochemistry was assigned on the basis of 1d-NOESY experiment.

Table 4.1 Ligand evaluation for the Ni-catalyzed cycloaddition[a]

entry	L_n ligand	**4** conversion[b]	**5** isolated yield[c]
1	PPh_3	49%	n.d.
2	DPPF	48%	n.d.
3	BINAP	-	n.d.
4	PCy_2Ph	60%	n.d.
5	$P(n\text{-}Bu)_3$	72%	23%
6	PCy_3	83%	37% (28%)[d]
7	$P(Cyp)_3$	81%	30%
8		18%	n.d.
9	**IPr**	**>99%**	**70%**[e]

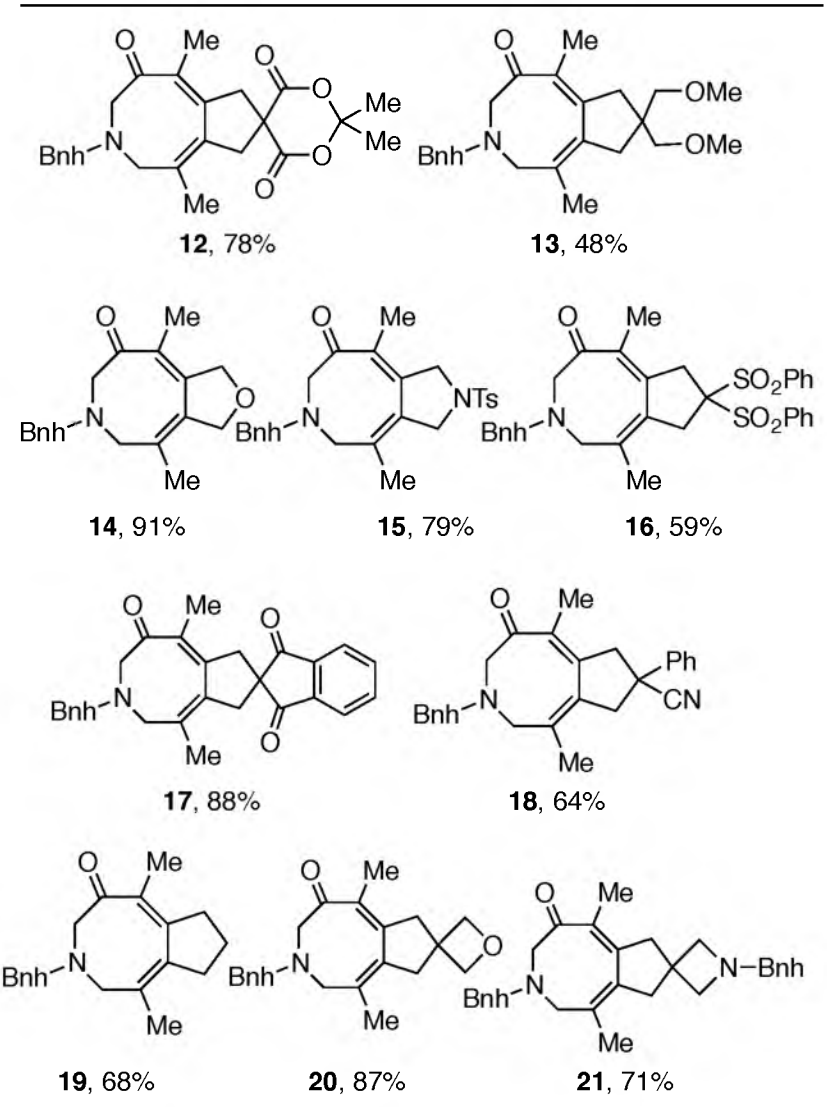
[a]Reaction conditions: azetidinone **4** (1 equiv, 0.1 M), diyne (1.2 equiv), 10 mol % $Ni(COD)_2$, ligand (20 mol % for entries 1,4-8; 10 mol % for entries 2,3 and 9), toluene, 100 °C, 12 h. [b]Conversion of diyne was determined by ^{1}HNMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [c]Yields of isolated product. [d]Solution of diyne **1** in toluene was added dropwise to the reaction mixture. [e]Reaction was run at RT.

Table 4.2 Temperature-effect evaluation on the Ni/IPr-catalyzed cycloaddition of diyne 1 and azetidinone 4[a]

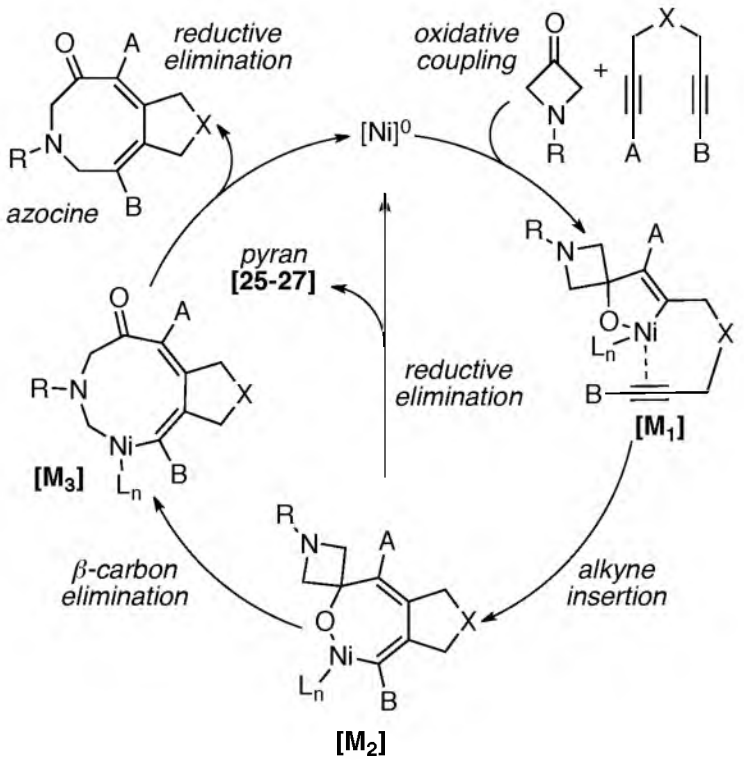
Entries	Conc.	Temp	Yield[b]
1	0.1 M	rt	70%
2	0.1 M	60 °C	35%
3	0.1 M	100 °C	21%
4	0.1 M	0 °C	84%
5	0.2 M	0 °C	68%
6	**0.05 M**	**0 °C**	**88%**

[a]Reaction conditions: azetidinone **4** (1 equiv), diyne **1** (1.2 equiv), 10 mol % $Ni(COD)_2$, 20 mol % IPr, toluene, 8 h. [b]Yield of isolated product **5**.

Scheme 4.1 Ni-catalyzed cycloaddition of diynes and azetidinone[a]



[a]Reaction conditions: benzhydryl azetidinone (1 equiv), diyne (1.2 equiv), 10 mol % $Ni(COD)_2$, 20 mol % IPr, toluene, 0 °C, 8 h.



For symmetrical diynes: A= B= Me
For unsymmetrical diynes: A = Me and B= H/OEt

Scheme 4.2 Proposed mechanism of the cycloaddition reaction

References

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CHAPTER 5

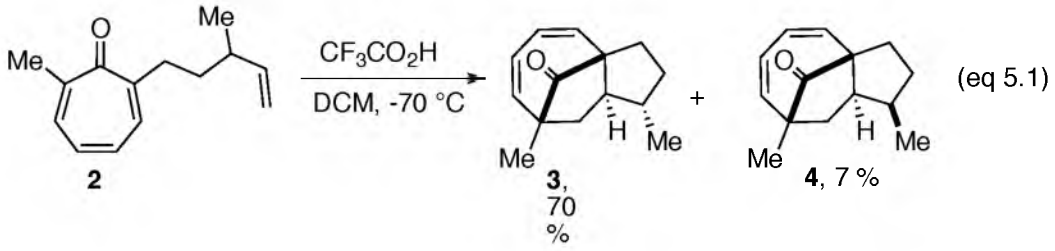
UNRAVELLING THE UNUSUAL MODE OF REACTIVITY OF TROPONE IN THE NICKEL-CATALYZED CYCLOADDITION WITH DIYNES

Introduction

Tropone, a nonbenzenoid aromatic has entertained scientists for more than six decades since its first report in 1945 (Figure 5.1).[1] Tropones have served as a readily available building block in various higher order cycloaddition reactions to afford the complex bridged motifs of a variety of natural products and other medicinally important compounds. The large orbital coefficients at the alpha-positions (and somewhat less so at the gamma positions) have made tropones a distinguished coupling partner in many higher order cycloaddition reactions.[2] Specifically, tropones undergo [6+2] cycloaddition with an alkene, as shown in eq 5.1.[3] Feldman and coworkers discovered that acidified tropones undergo [6+2] cycloaddition reaction in protic solvents to afford bicyclic-bridged eight-membered carbocycles **3**, and **4**. Taking advantage of the conjugated nature of tropones, Trost's group successfully developed a Pd-catalyzed [6+3] cycloaddition protocol that couples the tropones (e.g., **1**) with trimethylenemethane precursor (**5**) to access a nine-membered bridged carbocycles such as **6** (eq 5.2).[4]

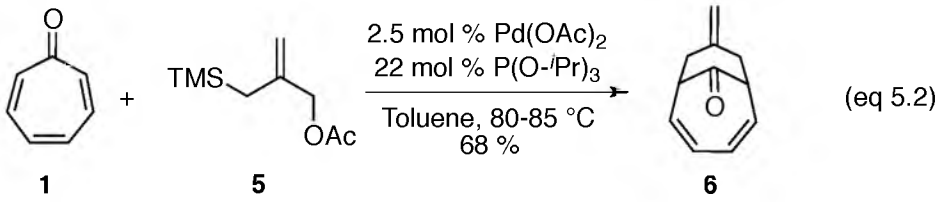
In another remarkable report by Woodward and Houk, tropone **1** undergoes [6+4] cycloaddition with a diene **7** to afford an exo-cycloadduct **8** (eq 5.3).[5] Besides using 6π electrons of a conjugated triene moiety (as mentioned previously), tropones can also participate in [8+2] and [8+3] cycloaddition reactions by using 8π electrons. Tropone **1** on reaction with diphenyl ketene **9** affords a [8+2] lactone cycloaddition product **10** (eq 5.4).[6] In 1981, Kanematsu disclosed an [8+3] cycloaddition mode of tropone **1**, wherein authors discovered that 2-oxallyl cation generated by the reaction of dibromo ketone **11** and Fe_2CO_9 reacts with tropone **1** to give a six-memebered lactone product **12** (eq 5.5).[7]

[6+2] Cycloaddition:



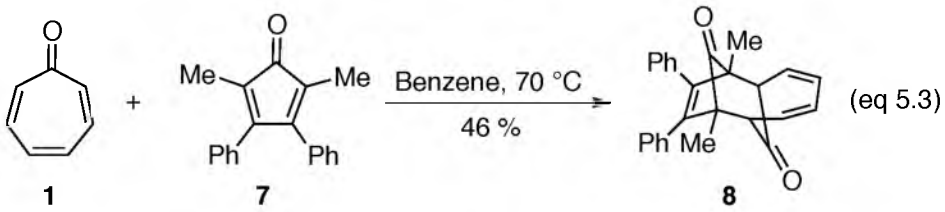
2 **3**, 70 % **4**, 7 %

[6+3] Cycloaddition:



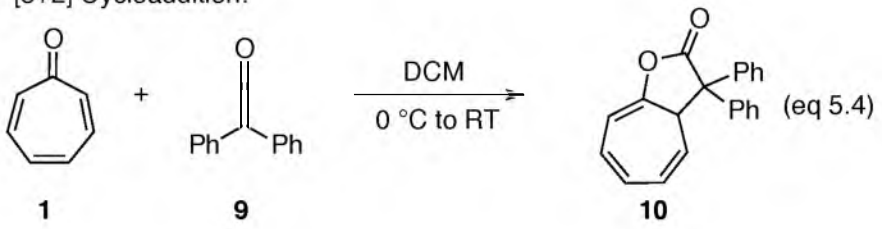
1 **5** **6**

[6+4] Cycloaddition:



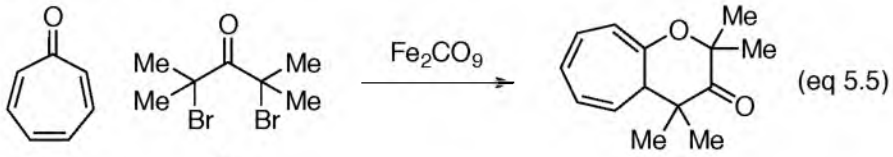
1 **7** **8**

[8+2] Cycloaddition:



1 9 10

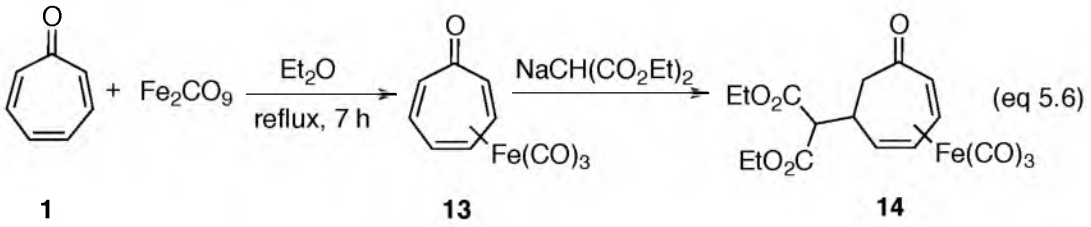
[8+3] Cycloaddition:



1 11 12

Given the prevalence of nonbridged seven-membered ring systems in other biologically relevant compounds, selective activation of a single C-C π bond in cycloaddition would greatly expand the synthetic utility of tropones.[8] Unfortunately, the inherent propensity to use 6π or 8π electrons to undergo higher order cycloaddition is difficult to overcome. Franck-Neumann[9] and Rigby[5d] addressed this problem by disrupting the conjugation by precomplexing tropone with iron-carbonyl. Tropones easily form η^4 complexes **13** with iron-carbonyls, which provide access to the enone moiety of tropone. This moiety can now be exploited for either conjugate addition of nucleophiles such as sodium diethyl malonate (eq 5.6) or it could also be used for Diels-Alder cycloaddition with dienes, as shown in Scheme 5.1. The iron-tropone complex **13** on reaction with diene **15** gives two diastereomers of 6-7 fused ring system (**16** and **17**, Scheme 5.1). The diene protecting group (i.e., the iron-carbonyl) can be easily removed to afford the desired organic product. Although this approach was successful in

exploiting one of the alpha-beta unsaturated double bonds of tropone, reactions required a stoichiometric amount of metal complexes as a pseudo-protecting group for the other two double bonds. Overcoming these challenges, we discovered a highly effective nickel catalyst that couples diynes with a single double bond of a tropone to selectively form fused bicyclic frameworks (vs bridged frameworks) *without the need for precomplexation*. Notably, this mode of cycloaddition maintains the integrity of tropone.



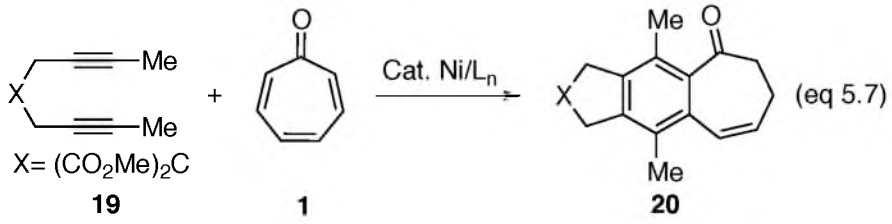
1 **13** **14**

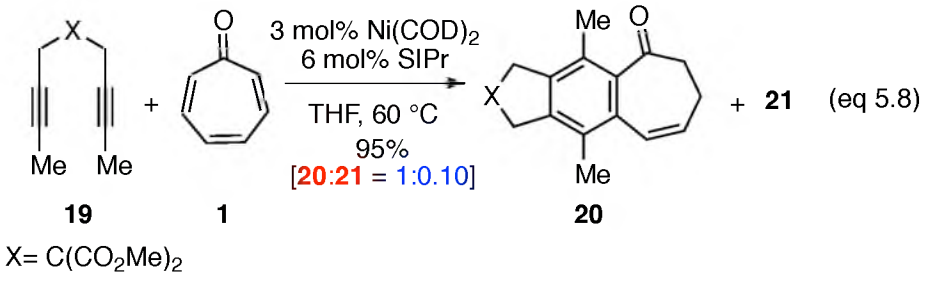
Results and discussion

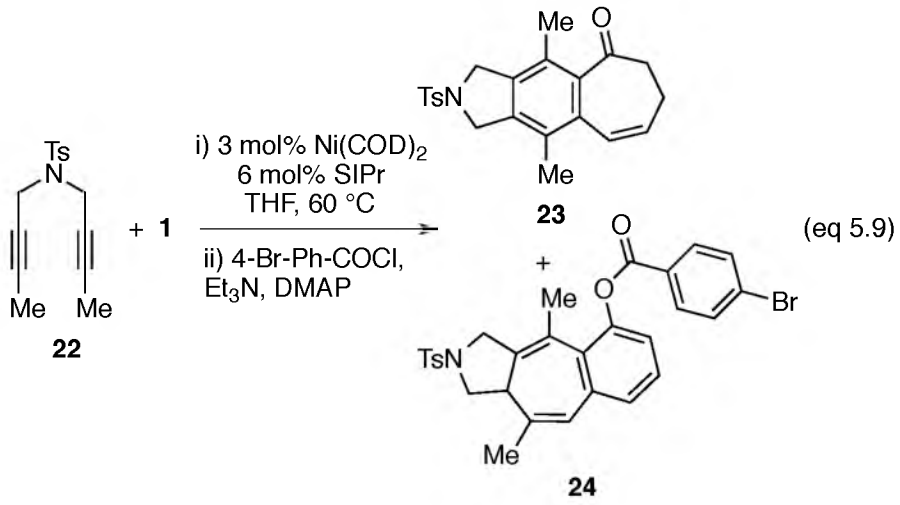
The nickel-catalyzed cycloaddition was investigated using diyne **19** and tropone **1** as model substrates (eq 5.7). Initially, a variety of monodentate and bidentate phosphines were screened. In most cases, dimerization of diyne was observed along with traces or low amount of the desired cycloadduct (Table 5.1, entry 1-10). However, when *N*-heterocyclic carbenes (NHCs) were explored as potential ligands, good to excellent yield of cycloadduct **20**, which couples the diyne with a *single C-C double bond* of the tropone selectively, was obtained (entries 11-14). Ultimately, SIPr proved to be the optimal ligand. I collaborated with Ashish Thakur for optimization as well as substrate scope studies related to this work. Further optimization led to our final reaction conditions: diyne (1 equiv), tropone (1.1 equiv), 3 mol % $Ni(COD)_2$, 6 mol % SIPr catalyst, THF, 60 °C, and 5 h. The model substrates afforded the desired product **20** along with another isomer **21** in excellent yield and >90% selectivity (for **20** determined by ^{1}HNMR

spectroscopy). Unfortunately, all attempts to elucidate the structure of **21** by NMR proved fruitless.[10] As such; we turned our attention to sulfonamide diyne **22** in an effort to obtain a crystalline minor isomer. Although the desired cycloadduct (**23**) was crystalline in nature (Figure 5.1), the minor isomer was an oily compound. However, acylation of minor isomer afforded *p*-bromo-benzoyl derivative (**24**) as a crystalline solid. The structure of **24** was unambiguously determined by single crystal X-ray crystallography. Surprisingly, **24** (and, therefore, minor isomer as well) has [5-7-6] ring fusion compared to [5-6-7] in case of major isomer, **23** (Figure 5.1).[11] Similar formation of minor phenolic products were also observed with other alkyl substituted diynes. The cycloaddition went smoothly with the diyne bearing a sulfone backbone, **25** (Table 5.2). Notably, this diyne is completely unreactive in several reported Ni-catalyzed cycloadditions.[12] Ni-catalysts have been reported to catalyze the cycloaddition of nitriles and diynes to form pyridines.[12b,d] Diyne having a nitrile group in the backbone selectively reacted with tropone **1** to afford the desired cycloadduct (**26**) in excellent yield. Based on Carreira's report, we recently introduced a spirocyclic oxetanyl diyne with a metabolically stable backbone.[13] The nickel-catalyzed reaction of this diyne with tropone, **1** afforded the desired cycloadduct **27** along with minor isomer, **27'** in good yield and good selectivity. The aryl-substituted internal diynes are one of the most challenging substrates in Ni/NHC-catalyzed cycloaddition reactions.[12a,b,d,14] Gratifyingly, the reaction of aryl-substituted symmetrical diynes with tropone afforded **28** and **29** in good yields. Interestingly, no minor cycloadduct (**28'** or **29'**) was obtained in these cases. To investigate the effect of electronics on the regioselectivity, we subjected an unsymmetrical phenyl-methyl diyne under standard reaction conditions; remarkably

exclusive formation of one regioisomer was detected (**30**). The regiochemistry of **30** was determined by NOESY-1D spectroscopy (for details, see experimental section). This regioselectivity outcome was also consistent with sulfonamide backbone diyne (**31**). The use of different aryl groups, i.e., 3,4-dimethoxyphenyl, and naphthyl, on alkyne termini is also possible, as demonstrated by entries **32** and **33**. Due to great interest in indole bearing novel compounds,[15] we synthesized and investigated indolyl-methyl diynes. To our delight the biaryl cycloadduct (**34**, **35**) were formed in very good yield and high regioselectivity. Interestingly, the regioselection was higher in case of 3-substituted indole diyne than 5-substituted indole diyne (**35** *vs* **34**). The retention of regioselectivity was observed when phenyl-ethyl, and phenyl-silyloxymethyl, diynes were subjected to standard reaction conditions (**36**, **37**).







(eq 5.9)

Interestingly, a diyne with a covalently bound δ-tocopherol can also be easily coupled with tropone **1** to afford regioselective cycloadduct, **38**.[12d] The unsymmetrical diyne bearing a gem-dimethyl group in the backbone reacted with tropone **1** to afford an exclusive regioisomer **39**. These findings suggest that regioselectivity is highly dependent on the substituents on the alkyne units of a diyne rather than backbone.[16] The cycloaddition of sterically unsymmetrical isopropyl-methyl diyne afforded product **40** where the bulkier group is next to the carbonyl of tropone (**40**). The phenolic isomer **40'** was also formed in a trace amount. In contrast, cycloaddition of phenyl-isopropyl diyne affords a product where the isopropyl unit is away from the carbonyl group (**41**), suggesting electronic factors override the steric factors (**19a**).

The lack of general methods to access troponoids prompted our investigation on the ability of converting the cycloadducts to fully aromatized products. Initially, conversion of cycloheptenone **23** to tropone **42** proved unsuccessful despite several attempts. Gratifyingly, we found that these compounds can be consistently converted to tropone by a three-step protocol.[17] The hydrogenation of alkene of **23** led to a saturated

cycloheptanone **42** that was then subjected to dibromination (**43**). Finally, di-dehydrobromination afforded the desired tropone, **44** (Scheme 5.2).

Mechanism

A proposed mechanism describing the formation of the cycloaddition product and the interesting side product is shown in Scheme 5.3. We believe that the origin of these outcomes lies in the course of rearrangement of cycloheptadienone **III**. Two pathways can form this intermediate: (a) homocoupling or (b) heterocoupling. In case of homocoupling, the diyne will undergo oxidative coupling on nickel (**I**) followed by tropone insertion that would lead to intermediate **II**. Alternatively, the oxidative coupling of tropone and one of the alkyne units (**III**) can take place first, and then insertion of another alkyne unit of the diyne would form nickelacycle **II**. The proposed intermediate **II** undergoes reductive elimination to afford the tricyclic product, **IV**. At this point, compound **IV** preferentially undergoes a sigmatropic shift to afford major product **V**. However, a minor pathway may involve the tautomerization of **IV** to cycloheptatrienol **VI** which would then undergo 6π electrocyclization to afford a bis-(divinyl)-cyclopropane intermediate, **VII**. This intermediate can either revert to **VI** or irreversibly rearrange to [5-7-6] fused intermediate **VIII**, which undergoes further sigmatropic shifts to yield the observed minor product, **IX**.

To gain more mechanistic insight into this interesting transformation, we collaborated with Xin Hong and Dr. K. N. Houk of UCLA. The computational studies suggested the homocoupling as a more favorable pathway over the heterocoupling. The tropone insertion in the nickelacycle **II** would take place in a different fashion than originally

proposed in Scheme 5.3, to afford intermediate **X**, which similarly transforms to the major product **IV**. Notably, in Scheme 5.3, we show that common intermediate **III** undergoes a series of transformations to afford the major and minor products. Computational studies suggest that minor product is formed by the isomerization of **X** rather than **III**. The ketone in intermediate **X** tautomerizes to enol form **XI**, which undergoes 6π electrocyclization to afford nickelacycle **XII**. This nickelacycle reductively eliminates to intermediate **VII**, which then transforms to the minor product.

Conclusion

In conclusion, we have discovered a nickel catalyst that can effectively and selectively incorporate a single C-C π bond of tropone in the cycloaddition with diyne. Additionally, we successfully converted the cycloadducts to useful troponoids. The mechanistic studies to understand this unique reactivity of tropone and further expansion of this chemistry are underway in our lab.

General experimental

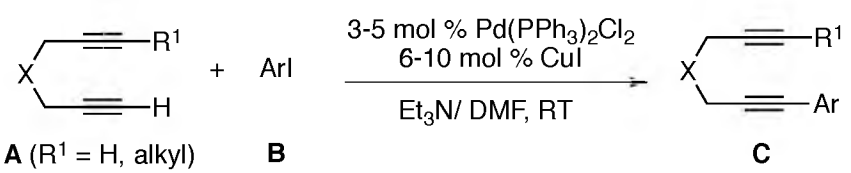
All reactions were conducted under an atmosphere of N_2 using standard Schlenk techniques or in a N_2-filled glove box unless otherwise noted. Toluene was dried over neutral alumina under N_2 using a Grubbs type solvent purification system. THF was freshly distilled from Na/benzophenone. $Ni(COD)_2$ was purchased from Strem and used without further purification. Sodium hydride was thoroughly washed with pentane and dried *in vacuo* prior to use. Tropone was purchased from Sigma-Aldrich and used as

received. Diynes were prepared according to reported literature procedure. All other reagents were purchased and used without further purification unless otherwise noted.

^{1}H and ^{13}C Nuclear Magnetic Resonance spectra of pure compounds were acquired at 400 and 100 MHz or 500 and 125 MHz, respectively, unless otherwise noted. All spectra are referenced to a singlet at 7.27 ppm for ^{1}H and to the central line of a triplet at 77.23 ppm for ^{13}C. The abbreviations s, d, dd, dt, dq, t, td, tq, q, qt, quint, sept, septd, septt, m, brm, brd, brt, and brs stand for singlet, doublet, doublet of doublets, doublet of triplets, doublet of quartets, triplet, triplet of doublets, triplet of quartets, quartet, quartet of triplets, quintet, septet, septet of doublets, septet of triplets, multiplet, broad multiplet, broad doublet, broad triplet, and broad singlet, in that order. All ^{13}C NMR spectra were proton decoupled. IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer.

Gas Chromatography was performed on an Agilent 6890 gas chomatograph with a 30 meter HP-5 column using the following conditions: initial oven temperature: 100 °C; temperature ramp rate 50 °C/min.; final temperature: 300 °C held for 7 minutes; detector temperature: 250 °C.

General procedure for the Sonogashira coupling in the syntheses of symmetrical and unsymmetrical diynes (G1)

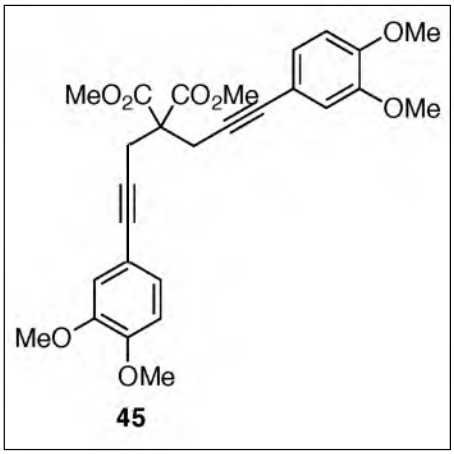


A (R^1 = H, alkyl) **B** **C**

In a nitrogen-filled glove box, a round bottomed flask (or a Schlenk tube under N_2) was charged with terminal diyne **A** (1.00 equiv), aryl iodide **B** (1.10-2.20 equiv), $Pd(PPh_3)_2Cl_2$ (0.03-0.05 equiv), and CuI (0.06-0.10 equiv.) in dry and degassed NEt_3 (2.4 ml/mmol of diyne) and dry dimethylformamide (1.2 ml/mmol of diyne), unless otherwise noted. The resulting reaction mixture was stirred at room temperature for an indicated period of time. The solvent was evaporated *in vacuo* and satd. NH_4Cl was added to the reaction mixture. The aqueous layer was extracted three times with ethyl acetate and the combined organic extract was washed with brine. The organic phase was collected, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The remaining residue was purified by silica gel flash column chromatography to yield pure unsymmetrical diyne **C**.

Dimethyl-2,2-bis(3-(3,4-dimethoxyphenyl)prop-2-yn-1-yl)malonate (**45**)

The general procedure **G1** was used with dimethyl-2,2-di(prop-2-yn-1-yl)malonate (333.0 mg, 1.60 mmol), 4-iodo-1,2-dimethoxybenzene[18] (929.50 mg, 3.52 mmol), $Pd(PPh_3)_2Cl_2$ (56.2 mg, 0.08 mmol), and CuI (30.5 mg, 0.16 mmol) in 3.7 ml of NEt_3 and 1.4 ml of DMF. The reaction mixture was stirred at room temperature for 16 h.



45

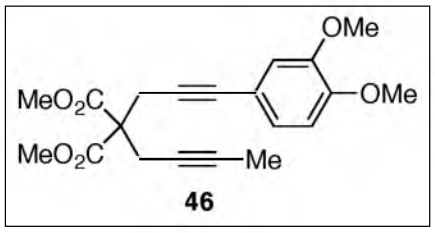
The remaining residue was purified by silica gel flash column chromatography using 45% ethyl acetate in hexanes (R_f = 0.27) to afford the title compound **7** (693.0 mg, 1.44 mmol) as an off-white solid in 90% yield. Mp: 132-134 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.99 (dd, J = 1.6, 8.0 Hz, 2H), 6.88 (d, J = 2.0 Hz, 2H), 6.78 (s, 1H), 6.76 (s, 1H), 3.87 (d, J = 3.2 Hz, 12H), 3.81 (s, 6H), 3.26 (s, 4H). ^{13}C

NMR (100 MHz, $CDCl_3$): δ (ppm) 169.7, 149.6, 148.8, 125.2, 115.5, 114.6, 111.1, 83.9, 82.5, 57.5, 56.12, 56.10, 53.3, 24.1. IR (CH_2Cl_2, cm^{-1}): 3002, 2955, 2836, 1739, 1578, 1441, 1077, 763, 622. HRMS (ESI+) calcd for $C_{27}H_{28}O_8Na$ $[M+Na]^+$ 503.1682, found 503.1685.

Dimethyl-2-(but-2-yn-1-yl)-2-(3-(3,4-dimethoxyphenyl)prop-2-yn-1-yl)malonate (**46**)

The general procedure **G1** was used with dimethyl-2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (223.2 mg, 1.00 mmol), 4-iodo-1,2-dimethoxybenzene (292.0 mg, 1.11 mmol), $Pd(PPh_3)_2Cl_2$ (35.3 mg, 0.05 mmol), and CuI (19.1 mg, 0.1 mmol) in 2.4 ml of NEt_3 and 1.2 ml of DMF.

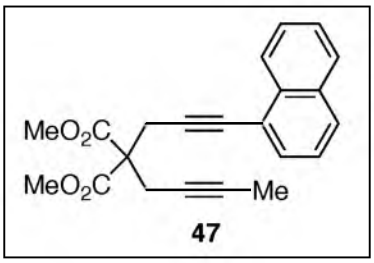


46

The reaction mixture was stirred at room temperature for 16 h. The remaining residue was purified by silica gel flash column chromatography using 25% ethyl acetate in hexanes (R_f = 0.31) to afford the title compound **46** (338.4 mg, 0.14 mmol) as a yellow oil in 94% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.93 (dd, J = 1.6, 8.4 Hz, 1H), 6.83 (d, J = 1.6 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 3.83 (d, J = 2.0 Hz, 6H), 3.74 (s, 6H), 3.15 (s, 2H), 2.95 (bq, J = 2.4 Hz, 2H), 1.74 (t, J = 2.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.7, 149.4, 148.6, 125.0, 115.5, 114.5, 111.0, 83.6, 82.5, 79.3, 73.1, 57.3, 56.0, 55.9, 53.0, 23.7, 23.3, 3.6. IR (CH_2Cl_2, cm^{-1}): 3004, 2955, 2839, 2256, 1741, 1600, 1439, 1074, 763, 649. HRMS (ESI+) calcd for $C_{20}H_{22}O_6Na$ $[M+Na]^+$ 381.1314, found 381.1323.

Dimethyl 2-(but-2-yn-1-yl)-2-(3-(naphthalen-1-yl)prop-2-yn-1-yl) malonate (**47**)

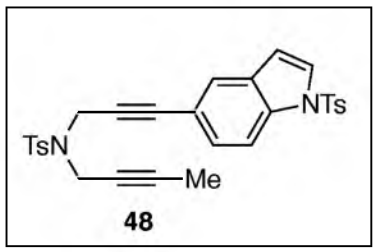


47

The general procedure **G1** was used with dimethyl-2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (329.5 mg, 1.48 mmol), 1-iodo-naphthalene (414.4 mg, 1.63 mmol), $Pd(PPh_3)_2Cl_2$ (52.0 mg, 0.07 mmol), and CuI (28.3 mg, 0.15 mmol) in 3.6 ml of NEt_3 and 1.8 ml of DMF. The reaction mixture was stirred at room temperature for 16 h. The remaining residue was purified by silica gel flash column chromatography using 20% ethyl acetate in hexanes (R_f = 0.42) to afford the title compound **47** (355.7 mg, 1.02 mmol) as a yellow oil in 69% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.28 (d, J = 8.4 Hz, 1H), 7.82 (dd, J = 8.4, 14.0 Hz, 2H), 7.63 (d, J = 6.4 Hz, 1H), 7.58 (td, J = 1.2, 6.4 Hz, 1H), 7.51 (td, J = 1.2, 8.4 Hz, 1H), 7.40 (dd, J = 7.2, 8.4 Hz, 1H), 3.82 (s, 6H), 3.38 (s, 2H), 3.10 (q, J = 2.4 Hz, 2H), 1.81 (t, J = 2.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.9, 113.6, 133.3, 130.7, 128.6, 128.4, 126.9, 126.5, 126.3, 125.3, 121.0, 89.2, 81.8, 79.6, 73.2, 57.4, 53.3, 24.3, 23.7, 3.8. IR (CH_2Cl_2, cm^{-1}): 3057, 3004, 2954, 2845, 2235, 1741, 1586, 1397, 1017, 776, 737. HRMS (ESI+) calcd for $C_{22}H_{20}O_4Na$ $[M+Na]^+$ 371.1259, found 371.1253.

N-(but-2-yn-1-yl)-4-methyl-*N*-(3-(1-tosyl-1*H*-indol-5-yl)prop-2-yn-1-yl)benzenesulfonamide (**48**)



48

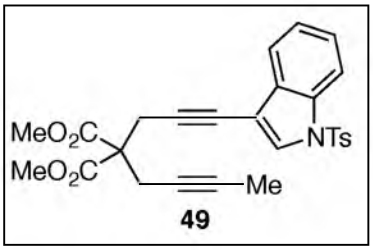
The general procedure **G1** was used with N-(but-2-yn-1-yl)-4-methyl-N-(prop-2-yn-1-yl)benzenesulfonamide (228.7 mg, 0.88 mmol), 5-iodo-1-tosyl-1-indole[19] (382.4 mg, 0.96 mmol), $Pd(PPh_3)_2Cl_2$ (31.0 mg, 0.04 mmol), and

CuI (17.0 mg, 0.09 mmol) in 2.0 ml of NEt_3 and 1.0 ml of DMF. The reaction mixture was stirred at room temperature for 24 h. The remaining residue was purified via silica gel flash column chromatography using 55% ethyl acetate in hexanes (R_f = 0.31) to afford the title compound **48** (374.0 mg, 0.71 mmol) as an off-white solid in 80% yield. Mp: 136-138 °C

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.88 (d, J = 8.4 Hz, 1H), 7.76 (m, 4H), 7.58 (d, J = 3.2 Hz, 1H), 7.38 (s, 1H), 7.25 (m, 4H), 7.13 (d, J = 8.4 Hz, 1H), 6.59 (d, J = 3.2 Hz, 1H), 4.39 (s, 2H), 4.15 (s, 2H), 2.36 (s, 3H), 2.32 (s, 3H), 1.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 145.4, 143.7, 135.8, 135.3, 134.5, 130.7, 130.2, 129.6, 128.21, 128.16, 127.6, 127.0, 125.1, 117.5, 113.6, 108.8, 85.9, 82.1, 81.1, 71.8, 37.3, 37.2, 21.8, 21.6, 3.7. IR (CH_2Cl_2, cm^{-1}): 3142, 2980, 2922, 2236, 1734, 1597, 1455, 1371, 1045, 629, 572. HRMS (ESI+) calcd for $C_{29}H_{26}N_2O_4NaS_2$ $[M+Na]^+$ 553.1232, found 553.1237.

Dimethyl-2-(but-2-yn-1-yl)-2-(3-(1-tosyl-1H-indol-3-yl)prop-2-yn-1-yl)malonate (**49**)

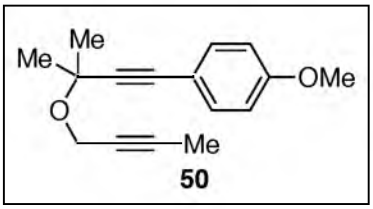
The general procedure **G1** was used with dimethyl-2-(but-2-yn-1-yl)-2-(prop-2-yn-1-yl)malonate (297.8 mg, 1.34 mmol), 3-iodo-1-tosyl-1-indole[20] (585.5 mg, 1.47 mmol), $Pd(PPh_3)_2Cl_2$ (47.0 mg, 0.07 mmol), and CuI (25.5 mg, 0.13 mmol) in 3.1 ml of NEt_3 and 1.5 ml of DMF. The reaction mixture was stirred at room temperature for 24 h. The remaining residue was purified by silica gel flash column chromatography using 25-35% ether in hexanes (R_f = 0.21) to afford the title compound **49** (478.1 mg, 0.98 mmol, mp: 46-48 °C) as a yellow solid in 73% yield.



49

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.95 (d, J = 7.2 Hz, 1H), 7.76 (d, J = 6.8 Hz, 2H), 7.65 (s, 1H), 7.57 (d, J = 6.8, 1H), 7.21-7.33 (m, 4H), 3.78 (s, 6H), 3.26 (s, 2H), 3.01 (s, 2H), 2.33 (s, 3H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.7, 145.5, 135.2, 134.3, 131.2, 130.2, 128.8, 127.1, 125.6, 123.9, 120.6, 113.7, 105.2, 88.7, 79.6, 74.7, 73.1, 57.3, 53.2, 24.1, 23.5, 21.7, 3.7. IR (CH_2Cl_2, cm^{-1}): 3140, 3005, 2955, 2923, 2259, 1748, 1597, 1445, 1004, 730, 606, 572. HRMS (ESI+) calcd for $C_{27}H_{25}NO_6NaS$ $[M+Na]^+$ 514.1300, found 365.1296.

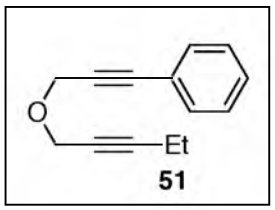
1-(3-(but-2-yn-1-yloxy)-3-methylbut-1-yn-1-yl)-4-methoxybenzene (**50**)



50

The general procedure **G1** was used with 3-(but-2-yn-1-yloxy)-3-methylbut-1-yne (243.0 mg, 1.78 mmol), 1-iodo-4-methoxybenzene (460.0 mg, 1.96 mmol), $Pd(PPh_3)_2Cl_2$ (37.6 mg, 0.05 mmol), and CuI (20.4 mg, 0.11 mmol) in 4.1 ml of NEt_3. The reaction mixture was stirred at room temperature for 24 h. The remaining residue was purified by silica gel flash column chromatography using 5-10% ether in hexanes (R_f = 0.27) to afford the title compound **50** (281.0 mg, 1.16 mmol) as a light yellow oil in 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 (bd, J = 8.8 Hz, 2H), 6.84 (bd, J = 8.8 Hz, 2H), 4.30 (q, J = 2.4 Hz, 2H), 3.82 (s, 3H), 1.86 (t, J = 2.4 Hz, 3H), 1.58 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 159.8, 133.4, 115.6, 114.1, 95.0, 89.2, 85.0, 81.9, 76.3, 71.5, 55.5, 53.2, 29.2, 4.0. IR (CH_2Cl_2, cm^{-1}): 2984, 2933, 2860, 2241, 1714, 1606, 1463, 1151, 1045, 891, 558. HRMS (ESI+) calcd for $C_{16}H_{18}O_2Na$ $[M+Na]^+$ 265.1204, found 265.1205.

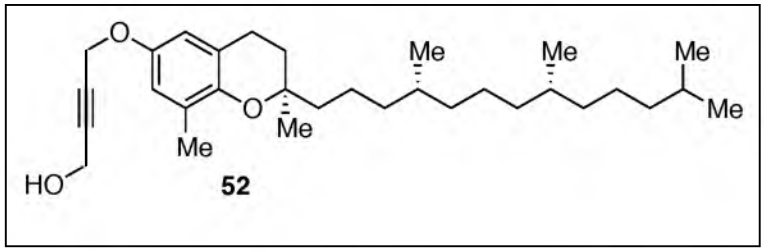
3-(pent-2-yn-1-yloxy)prop-1-yn-1-yl)benzene (**51**)



51

To a suspension of prewashed and dried NaH (98.0 mg, 4.10 mmol) in THF (8.5 ml) was added dropwise a solution of 3-phenylprop-2-yn-1-ol (472.0 mg, 3.60 mmol) at 0 °C. The resulting solution was stirred for 45 min and then 1-bromopent-2-yne (500.0 mg, 3.40 mmol) was added and stirred overnight. The reaction was quenched by the addition of satd. NH_4Cl and the aqueous phase was extracted three times with ether. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The remaining residue was purified by silica gel flash column chromatography using 2% ether in pentane (R_f = 0.5) to afford the title compound **51** (640.3 g, 3.23 mmol) as yellow oil in 95% yield. The spectral data were consistent with the reported literature.[21]

4-(((R)-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)but-2-yn-1-ol (**52**)



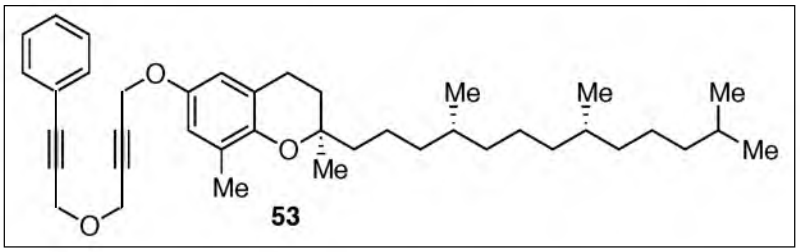
52

To a suspension of prewashed and dried NaH (146.00 mg, 6.08 mmol) in THF (10 ml) was added dropwise a solution of d-tocopherol (1.75 g, 4.35 mmol) in tetrahydrofuran (4.5 ml) at 0 °C. The resulting yellow solution was stirred for 45 min and then ((4-bromobut-2-yn-1-yl)oxy)(tert-butyl)dimethylsilane[22] (1.26 g, 4.78 mmol) was added and stirred overnight. The reaction was quenched by the addition of satd. NH_4Cl and the aqueous phase was extracted three times with ether. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product obtained was dissolved in

THF (10 ml) and tetra-*n*-butylammonium fluoride soln. (4.57 ml, 4.57 mmol, 1 M in THF) was added dropwise at room temperature under nitrogen atmosphere. The resulting solution was stirred overnight at room temperature. The reaction was quenched by the addition of water and satd. $NaHCO_3$ solution. The aqueous phase was extracted with ether, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The remaining residue was purified by silica gel flash column chromatography using 15-25% ether in hexanes (R_f = 0.18) to afford the title compound **52** (1.21 g, 2.57 mmol) as a yellow oil in 59% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.64 (d, J = 2.0 Hz, 1H), 6.53 (d, J = 2.0 H, 1H), 4.64 (s, 2H), 4.30 (s, 2H), 2.74 (t, J = 5.2 Hz, 2H), 2.18 (s, 3H), 0.88-1.81 (m, 39H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 150.4, 147.1, 127.5, 121.2, 116.1, 112.7, 90.0, 85.2, 81.7, 75.9, 57.0, 51.5, 40.3, 39.6, 37.69, 37.66, 37.5, 33.0, 32.9, 31.5, 28.2, 25.0, 24.7, 24.4, 22.9, 22.8, 21.2, 20.0, 19.9, 16.4. IR (CH_2Cl_2, cm^{-1}): 3059, 2927, 2863, 1604, 1479, 1377, 1347, 1079, 755, 691, 585. HRMS (ESI+) calcd for $C_{31}H_{50}O_3Na$ $[M+Na]^+$ 493.3658, found 493.3668.

(R)-2,8-dimethyl-6-((4-((3-phenylprop-2-yn-1-yl)oxy)but-2-yn-1-yl)oxy)-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman (**53**)

To a stirring suspension of prewashed and dried NaH (17.40 mg, 0.72 mmol) in THF (2.0 ml) was added dropwise a solution of **52** (262.30 mg, 0.56 mmol) in THF (0.8 ml) at 0 °C. The resulting yellow solution was stirred for 45 min and then (3-bromoprop-1-yn-1-yl)benzene (113.00 mg, 0.59 mmol) was added and stirred overnight. The reaction was

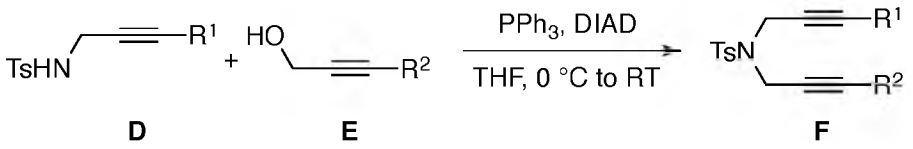


53

quenched by the addition of satd. NH_4Cl and the aqueous phase was extracted three times with ether. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The remaining residue was purified by silica gel flash column chromatography using 15-25% ether in hexanes (R_f = 0.18) to afford the title compound **53** (195.70 g, 0.34 mmol) as a yellow oil in 60% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 (m, 2H), 7.32 (m, 3H), 6.64 (d, J = 2.8 Hz, 1H), 6.53 (d, J = 2.8Hz, 1H), 4.66 (t, J = 2.0 Hz, 2H), 4.46 (s, 2H), 4.38 (t, J = 2.0 Hz, 2H), 2.73 (m, 2H), 2.15 (s, 3H), 0.84-1.83 (m, 38H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 150.4, 147.1, 132.0, 128.7, 128.5, 127.5, 122.7, 121.2, 116.2, 112.8, 87.0, 84.4, 82.8, 82.4, 75.9, 57.5, 57.1, 57.0, 40.3, 39.6, 37.7, 37.6, 37.5, 33.0, 32.9, 31.5, 28.2, 25.0, 24.7, 24.3, 22.94, 22.91, 22.8, 21.2, 20.0, 19.9, 16.4. IR (CH_2Cl_2, cm^{-1}): 2927, 2361, 1650, 1558, 1541, 1478, 1222, 757, 690. HRMS (ESI+) calcd for $C_{40}H_{56}O_3Na$ $[M+Na]^+$ 607.4127, found 607.4131.

General procedure for the Mitsunobu reaction for the syntheses of diynes **54** and **55** (G2)

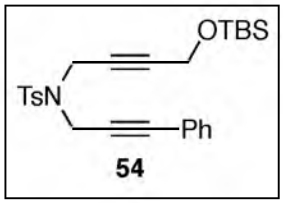


D **E** **F**

To a stirring solution of tosylamide **D** (1.00 equiv), PPh_3 (1.20 equiv), and propargyl alcohol **E** (1.10 equiv) in THF (4.6 ml/mmol of **D**) at 0 °C, was added dropwise DIAD (1.10 equiv.) for 20 min. The resulting solution was warmed to room temperature and continued stirring for 24 h at the same temperature. Silica gel was added and solvent was

evaporated *in vacuo* and the remaining residue was directly purified by silica gel flash chromatography to yield pure diyne **F**.

N-(4-((tert-butyldimethylsilyl)oxy)but-2-yn-1-yl)-4-methyl-N-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (**54**)

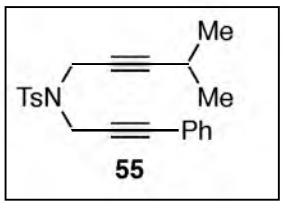


54

The general procedure **G2** was used with 4-methyl-N-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (403.50 mg, 1.41 mmol), PPh_3 (445.60 mg, 1.70 mmol), 4-((tert-butyldimethylsilyl)oxy)but-2-yn-1-ol[13] (312.00 mg, 1.56 mmol), and DIAD (314.40 mg, 1.56 mmol) in THF (6.5 ml). The resulting solution was warmed to room temperature and continued stirring for 24 h. The remaining residue was purified by silica gel flash column chromatography using 5-15% ether in hexanes (R_f = 0.30) to afford the title compound **54** (496.00 mg, 1.06 mmol, mp: 65-66 °C) as a colorless solid in 75 % yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.76 (d, J = 8.4 Hz, 2H), 7.24-7.30 (m, 5H), 7.17 (m, 2H), 4.40 (s, 2H), 4.23 (bt, J = 1.6 Hz, 2H), 4.21 (t, J = 1.6 Hz, 2H), 2.37 (s, 3H), 0.89 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 144.0, 135.6, 131.8, 129.7, 128.7, 128.4, 128.2, 122.4, 86.0, 84.7, 81.6, 51.8, 37.4, 37.1, 26.0, 21.7, 18.5, -5.0. IR (CH_2Cl_2, cm^{-1}): 3061, 2954, 2930, 2857, 2244, 1917, 1807, 1598, 1467, 1215, 1004, 779, 715. HRMS (ESI+) calcd for $C_{26}H_{33}NO_3NaSSi$ $[M+Na]^+$ 490.1848, found 490.1853.

4-methyl-N-(4-methylpent-2-yn-1-yl)-N-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (**55**)



55

The general procedure **G2** was used with 4-methyl-N-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (637.00 mg, 2.23 mmol), PPh_3 (703.60 mg, 2.68 mmol), 4-methylpent-2-yn-1-ol[23]

(241.00 mg, 2.46 mmol), and DIAD (497.30 mg, 2.46 mmol) in THF (10.3 ml). The resulting solution was warmed to room temperature and stirred for 24 h. The remaining residue was purified by silica gel flash column chromatography using 10-20% ether in hexanes (R_f = 0.30) to afford the title compound **55** (571.00 mg, 1.56 mmol) as a colorless oil in 70 % yield.

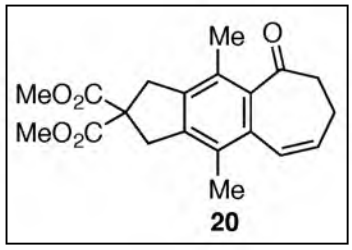
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.73 (d, J = 8.0 Hz, 1H), 7.21-7.26 (m, 5H), 7.17 (m, 2H), 4.36 (s, 2H), 4.16 (bd, J = 2.0 Hz, 2H), 2.39 (m, 1H), 2.33 (s, 3H), 1.01 (d, J = 7.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 143.8, 135.7, 131.8, 129.7, 128.6, 128.3, 128.1, 122.5, 92.1, 85.6, 81.9, 71.7, 37.5, 37.18, 37.16, 22.8, 21.6, 20.5. IR (CH_2Cl_2, cm^{-1}): 3060, 2972, 2929, 2874, 2250, 1598, 1492, 1120, 950, 757, 575. HRMS (ESI+) calcd for $C_{22}H_{23}NO_2NaS$ $[M+Na]^+$ 388.1347, found 388.1355.

General procedure for Ni-catalyzed cycloaddition of diynes and tropone (G3)

In a nitrogen-filled glove box, 3 mol % catalyst solution (prepared from Ni $(COD)_2$ and SIPr in 1:2 molar ratio in THF) was added to solution of diyne (1.00 equiv, 0.1 M) and tropone (1.1 equiv) in THF at room temperature. The resulting reaction mixture was then brought out of the glove box, sealed, and stirred for the indicated period of time at RT or 60 °C (unless otherwise noted). The reaction was opened to air, concentrated *in vacuo,* and purified by silica gel flash column chromatography.

Dimethyl-4,10-dimethyl-5-oxo-3,5,6,7-tetrahydrocyclohepta[*f*]indene-2,2(1*H*)-dicarboxylate (**20**) and dimethyl-5-hydroxy-4,10-dimethyl-1,10a-dihydrobenzo[*f*]azulene-2,2(3*H*)-dicarboxylate (**21**)

The general procedure **(G3)** was used with 43.20 mg (0.18 mmol) of malonate diyne, 21.30 mg (0.20 mmol) of tropone, and 3 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue

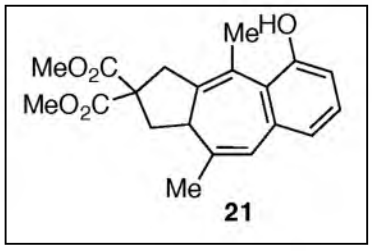


20

was purified by flash column chromatography using 20% ethyl acetate in hexanes (R_f = 0.25) to afford the title compound **20** (49.00 mg, 0.14 mmol) as a pale yellow oil and an inseparable mixture of **20** and minor isomer **21** (10.60 mg, 0.03 mmol) as a light brown oil, in 95% yield.

[20]: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.54 (d, J = 11.2 Hz, 1H), 6.20 (dt, J = 7.0, 11.2 Hz, 1H), 3.76 (s, 6H), 3.57 (s, 2H), 3.56 (s, 2H), 2.92 (t, J = 6.8 Hz, 2H), 2.34 (q, J = 6.8 Hz, 2H), 2.15 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 208.7, 172.2, 140.3, 139.6, 138.9, 132.5, 131.3, 129.4, 128.7, 127.7, 59.2, 53.2, 50.2, 40.4, 40.3, 23.0, 16.7, 15.9. IR (CH_2Cl_2, cm^{-1}): 2954, 1737, 1688, 1436, 1254, 1165. HRMS (ESI+) calcd for $C_{20}H_{23}O_3Na$ $[M+Na]^+$ 365.1365, found 365.1373.

[21]: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.08 (t, J = 7.6 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 6.68 (dd, J = 1.2, 8.0 Hz, 1H), 6.38 (s, 1H), 4.97 (brs, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.10 (m, 2H), 2.77-2.67 (m, 2H), 2.64 (dd, J = 4.0, 11.2 Hz, 1H), 2.07 (s, 3H), 1.96 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 172.48, 172.46, 153.2, 145.4, 144.1, 138.2, 128.6, 126.5, 125.4, 121.8, 121.6, 113.2, 60.5, 53.2, 53.1, 42.3, 39.2, 35.4, 22.5. IR (CH_2Cl_2, cm^{-1}): 3389, 2924, 2853, 1736, 1457, 1264, 1071, 738. HRMS (ESI+) calcd for $C_{20}H_{22}O_5Na$ $[M+Na]^+$ 365.1365, found 365.1383.

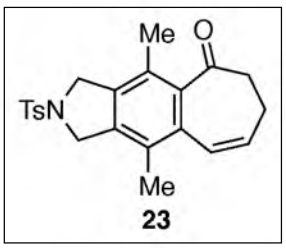


21

4,10-dimethyl-2-tosyl-2,3,6,7-tetrahydrocyclohepta[*f*]isoindol-5(1*H*)-

one [**23**] and 4,10-dimethyl-2-tosyl-1,2,3,10a-tetrahydrobenzo [4,5]cyclohepta[1,2-*c*]pyrrol-5-yl4-bromo-benzoate [**24**]

The general procedure **(G3)** was used with 103.00 mg (0.37 mmol) of sulfonamide diyne, 43.70 mg (0.41 mmol) of tropone, and 3 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The resulting reaction mixture was filtered through a short pad of silica and washed with dichloromethane. The filtrate was collected and concentrated *in vacuo*. The remaining residue was dissolved in 1.9 ml of dichloromethane and stirred at 0 °C in an ice bath. To this solution was added 24.60 mg (0.11 mmol) of *p*-bromobenzoyl chloride, 1.40 mg of 4-dimethylaminopyridine, followed by 15.20 mg of NEt_3 (0.15 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by addition of H_2O and aq. sat. NH_4Cl soln. and the aqueous phase was extracted three times with dichloromethane. The combined organic layers were collected, dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The crude product was purified by flash column chromatography using 30-45% ether in hexanes to afford the title compound **23** (28.50 mg, 0.05 mmol, decomposition > 230 °C, R_f = 0.33 in 35% ether/hexanes) as a light yellow solid and compound **23** (105.10 mg, 0.28 mmol, decomposition > 210 °C, R_f = 0.25 in 40% ether/hexanes) as an off-white solid, in 87% yield.

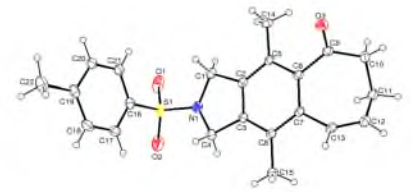


23

[23]: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.79 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 6.51 (d, J = 10.8 Hz, 1H), 6.23 (dt, J = 6.8, 10.8 Hz, 1H), 4.61 (s, 2H), 4.60 (s, 2H), 2.92 (t, J = 6.8 Hz, 2H), 2.42 (s, 3H), 2.34 (q, J = 6.8 Hz, 2H), 2.09 (s, 6H). ^{13}C NMR (100 MHz , $CDCl_3$): δ (ppm) 207.9, 143.9, 140.3, 136.7, 135.3, 134.0, 133.3,

132.3, 130.1, 128.7, 127.8, 127.7, 127.0, 54.0, 50.0, 23.1, 21.7, 16.5, 15.8. IR (CH_2Cl_2, cm^{-1}): 2925, 1451, 1345, 1164, 1110, 667. HRMS (ESI+) calcd for $C_{22}H_{23}NO_3NaS$ $[M+Na]^+$ 404.1296, found 404.1301.

The crystals suitable for crystallographic analysis were grown using THF and hexanes as solvents.

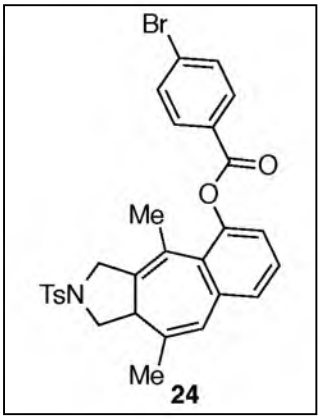


Crystal data and structure refinement for **23**

Empirical formula	C22 H23 N O3 S	
Formula weight	381.47	
Temperature	150(1) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	***P*** $2_1/n$	
Unit cell dimensions	a = 8.16640(10) Å	a= 90°.
	b = 26.8552(4) Å	b= 105.3641(9)°.
	c = 8.76720(10) Å	g = 90°.
Volume	1854.02(4) $Å^3$	
Z	4	
Density (calculated)	1.367 Mg/m^3	
Absorption coefficient	0.198 mm^{-1}	

F(000)	808
Crystal size	0.25 x 0.23 x 0.13 mm^3
Theta range for data collection	2.53 to 27.48°.
Index ranges	-10<=h<=10, -34<=k<=34, -11<=l<=11
Reflections collected	8416
Independent reflections	4261 [R(int) = 0.0207]
Completeness to theta = 27.48°	100.0 %
Absorption correction	Multi-scan
Max. and min. transmission	0.9748 and 0.9522
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4261 / 0 / 326
Goodness-of-fit on F^2	1.021
Final R indices [I>2sigma(I)]	R1 = 0.0423, wR2 = 0.1076
R indices (all data)	R1 = 0.0630, wR2 = 0.1204
Extinction coefficient	0.0127(15)
Largest diff. peak and hole	0.273 and -0.445 e.$Å^{-3}$

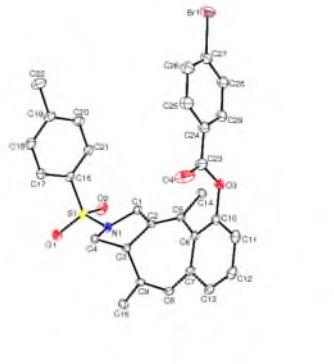
[24]: ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 8.01 (dd, *J* = 2.0, 6.5 Hz, 2H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.63 (dt, *J* = 2.5, 8.0 Hz, 2H), 7.34 (d, *J* = 7.5 Hz, 2H), 7.24 (d, *J* = 7.0 Hz, 1H), 7.18 (dd, *J* = 1.0, 8.0 Hz, 1H), 6.97 (dd, *J* = 1.5, 8.0 Hz, 1H), 6.42 (s, 1H), 4.17 (d, *J* = 14.0 Hz, 1H), 3.97 (d, *J* = 10.0 Hz, 1H), 3.38 (d, 14.5 Hz, 1H), 2.89 (dd, *J* = 6.5, 9.5 Hz, 1H), 2.43 (bs, 4H), 2.13 (s, 3H), 1.83 (d, *J* = 1.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ



24

(ppm) 164.5, 148.3, 144.1, 144.0, 140.0, 138.2, 133.2, 132.3, 132.0, 131.9, 130.0, 129.2, 128.6, 128.3, 127.4, 126.6, 125.0, 121.2, 120.2, 50.4, 50.1, 42.0, 21.8, 19.8, 19.5. IR (CH_2Cl_2, cm^{-1}): 2927, 2287, 1553, 1737, 1591, 1553, 1224, 1012, 673, 549. HRMS (ESI+) calcd for $C_{29}H_{26}NO_4NaSBr$ $[M+Na]^+$ 586.0664, found 586.0667.

The crystals suitable for crystallographic analysis were grown using dichloromethane and hexanes as solvents.



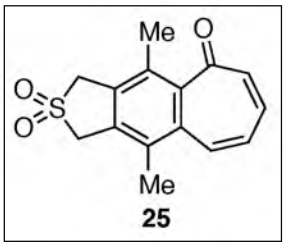
Crystal data and structure refinement for **24**

Empirical formula	C29 H26 Br N O4 S	
Formula weight	564.48	
Temperature	150(1) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	***P***	
Unit cell dimensions	a = 10.7009(1) Å	á= 95.2769(8)°.
	b = 11.9592(2) Å	â= 111.3317(10)°.
	c = 12.0410(2) Å	ã = 110.8436(9)°.
Volume	1297.32(3) $Å^3$	
Z	2	

Density (calculated)	1.445 Mg/m^3
Absorption coefficient	1.701 mm^{-1}
F(000)	580
Crystal size	0.40 x 0.28 x 0.20 mm^3
Theta range for data collection	2.23 to 27.53°.
Index ranges	-13<=h<=13, -15<=k<=15, -15<=l<=15
Reflections collected	11304
Independent reflections	5941 [R(int) = 0.0191]
Completeness to theta = 27.53°	99.4 %
Absorption correction	Multi-scan
Max. and min. transmission	0.7273 and 0.5495
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5941 / 0 / 328
Goodness-of-fit on F^2	1.023
Final R indices [I>2sigma(I)]	R1 = 0.0347, wR2 = 0.0854
R indices (all data)	R1 = 0.0483, wR2 = 0.0920
Largest diff. peak and hole	0.454 and -0.602 $e.Å^{-3}$

4,10-dimethyl-6,7-dihydro-1*H*-cyclohepta[4,5]benzo[1,2-*c*]thiophen-5(3*H*)-one-2,2-dioxide (**25**)

The general procedure **(G3)** was used with 30.90 mg (0.18 mmol) of sulfone backbone diyne, 21.20 mg (0.12 mmol) of tropone, and 3 mol % of catalyst in THF. The reaction mixture

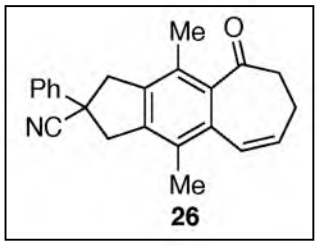


25

was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 70% ether in hexanes (R_f = 0.24) to afford the title compound **25** (27.60 mg, 0.10 mmol) as a colorless solid and an inseparable mixture of **25** and **25'** (6.00 mg, 0.02 mmol) as yellow oil, in 67% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.56 (d, *J* = 10.8 Hz, 1H), 6.32 (dt, *J* = 6.8, 10.8 Hz, 1H), 4.36 (d, *J* = 4.4 Hz, 4H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.39 (q, *J* = 6.8 Hz, 2H), 2.17 (d, *J* = 6.0 Hz, 6H). ^{13}C NMR (100 MHz , $CDCl_3$): δ (ppm) 207.5, 141.0, 133.9, 133.2, 132.0, 130.7, 130.3, 129.3, 128.8, 57.03, 57.0, 50.4, 22.9, 17.6, 16.8. IR (CH_2Cl_2, cm^{-1}): 2967, 2926, 1690, 1445, 1129, 829, 731, 605. HRMS (ESI+) calcd for $C_{15}H_{17}O_3S$ $[M+H]^+$ 277.0898, found 277.0896.

4,10-dimethyl-5-oxo-2-phenyl-1,2,3,5,6,7-hexahydrocyclohepta[*f*]indene-2-carbonitrile (**26**)



26

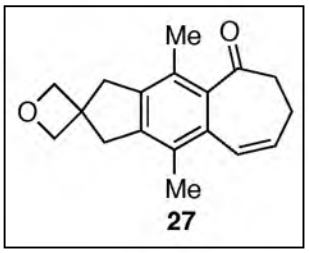
The general procedure **(G3)** was used with 41.90 mg (0.19 mmol) of phenyl-nitrile backbone diyne, 22.10 mg (0.21 mmol) of tropone, and 3 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 15% ethyl acetate in hexane (R_f = 0.25) to afford the title compound **26** (41.70 mg, 0.13) as a light yellow semisolid and an inseparable mixture of **26** and **26'** (18.2 mg, 0.06 mmol) as yellow oil, in 97% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.49 (m, 2H), 7.38 (m, 3H), 6.59 (d, *J* = 10.8 Hz, 1H), 6.26 (dt, *J* = 6.8, 10.8 Hz, 1H), 3.82 (dd, *J* = 6.8, 16.4 Hz, 2H), 3.51 (dd, *J* = 4.0, 16.4 Hz, 2H), 2.98 (t, *J* = 6.8 Hz, 2H), 2.41 (m, 2H), 2.18 (s, 6H). ^{13}C NMR (100 MHz,

$CDCl_3$): δ (ppm) 208.6, 140.5, 140.3, 139.8, 138.4, 133.3, 131.9, 129.34, 129.26, 129.2, 128.4, 128.1, 125.8, 124.6, 50.3, 47.1, 47.0, 46.2, 23.1, 16.9, 16.1. IR (CH_2Cl_2, cm^{-1}): 2927, 2235, 1686, 1444, 1125, 738. HRMS (ESI+) calcd for $C_{23}H_{21}NO_3Na$ $[M+Na]^+$ 350.1521, found 350.1529.

4,10-dimethyl-6,7-dihydro-1*H*-spiro[cyclohepta[*f*]indene-2,3'-oxetan]-5(3*H*)-one (**27**)

The general procedure **(G3)** was used with 28.10 mg (0.17 mmol) of oxetanyl diyne, 20.20 mg (0.19 mmol) of tropone, and 3 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 40-70% ether in hexanes (R_f = 0.20) to afford the title compound **27** (23.70 mg, 0.09 mmol, mp: 152-154 °C) as an off-white solid and an inseparable mixture of **27** and **27'** (16.90 mg, 0.06 mmol) as yellow oil, in 87% yield.



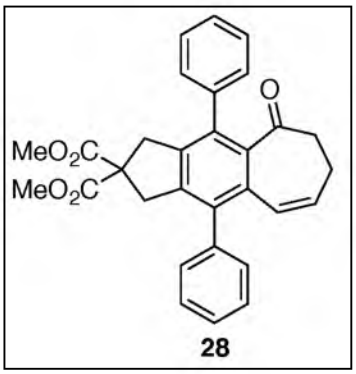
27

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.56 (d, *J* = 10.8 Hz, 1H), 6.20 (dt, *J* = 6.4, 10.8 Hz, 1H), 4.69 (s, 4H), 3.24 (d, *J* = 5.2 Hz, 4H), 2.94 (t, *J* = 6.8 Hz, 2H), 2.36 (q, *J* = 6.8 Hz, 2H), 2.17 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 208.9, 142.1, 140.7, 139.5, 132.3, 131.3, 129.5, 129.0, 128.0, 84.3, 50.3, 45.9, 44.0, 43.8, 23.1, 16.9, 16.0. IR (CH_2Cl_2, cm^{-1}): 3029, 2927, 2861, 1684, 1440, 1334, 1181, 1122, 834, 797, 737. HRMS (ESI+) calcd for $C_{18}H_{21}O_2$ $[M+H]^+$ 269.1542, found 269.1540.

Dimethyl-5-oxo-4,10-diphenyl-3,5,6,7-tetrahydrocyclohepta[*f*]indene-2,2(1*H*)-dicarboxylate (**28**)

The general procedure **(G3)** was used with 55.30 mg (0.15 mmol) of diphenyl malonate diyne, 17.90 mg (0.17 mmol) of tropone, and 3 mol % of catalyst in THF. The

reaction mixture was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 15% ethyl acetate in hexanes (R_f = 0.25) to afford the title compound **28** (45.7 mg, 0.98 mmol, mp = 164-166 °C) as a colorless solid in 64% yield.

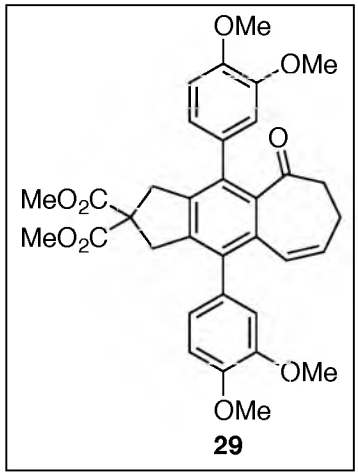


28

^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.47-7.37 (m, 5H), 7.36-7.29 (m, 3H), 7.26-7.23 (m, 2H), 6.17 (d, J = 11.0 Hz, 1H), 6.03 (dt, J = 6.5, 11.0 Hz, 1H), 3.70 (s, 6H), 3.47 (s, 2H), 3.42 (s, 2H), 2.91 (t, J = 7.0 Hz, 2H), 2.54 (q, J = 7.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 207.3, 172.0, 140.6, 139.2, 138.8, 138.4, 136.4, 135.7, 132.0, 131.3, 130.1, 129.6, 128.9, 128.62, 128.56, 127.64, 127.57, 59.8, 53.2, 50.2, 40.9, 40.7, 23.7. IR (CH_2Cl_2, cm^{-1}): 2954, 1736, 1692, 1436, 1200, 1072, 732, 702. HRMS (ESI+) calcd for $C_{30}H_{26}O_5Na$ $[M+Na]^+$ 489.1678, found 489.1685.

Dimethyl-4,10-bis(3,4-dimethoxyphenyl)-5-oxo-3,5,6,7-tetrahydrocyclohepta[f]indene-2,2(1H)-dicarboxylate (**29**)

The general procedure **(G3)** was used with 57.60 mg (0.12 mmol) of diaryl malonate diyne, 14.00 mg (0.13 mmol) of tropone, and 10 mol % of catalyst in THF. The reaction mixture was stirred at room temperature for 24 h. The remaining residue was purified by flash column chromatography using 60% ethyl acetate in hexanes (R_f = 0.25) to afford the title compound **29** (50.72 mg, 0.09 mmol) as a light yellow semisolid in 72% yield.

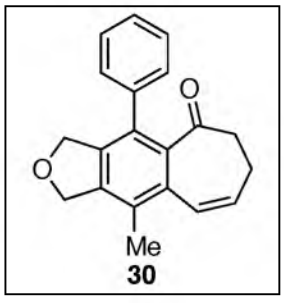


29

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.95 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 6.79 (m, 4H), 6.23 (d, J = 10.8 Hz, 1H), 6.02 (dt, J = 6.4, 11.2 Hz, 1H), 3.94 (s, 3H), 3.90 (d, J = 4.0 Hz, 6H), 3.88 (s, 3H), 3.70 (s, 6H), 3.48 (s, 2H), 3.44 (s, 2H), 2.91 (t, J = 6.8 Hz, 2H), 2.54 (q, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 207.4, 172.0, 149.0, 148.9, 148.6, 140.8, 140.7, 139.1, 136.2, 135.2, 132.0, 131.7, 131.0, 130.9, 130.3, 122.0, 121.2, 113.0, 112.6, 111.4, 111.3, 59.9, 56.19, 56.15, 56.12, 56.02, 53.2, 50.0, 41.0, 40.8, 29.9, 23.8. IR (CH_2Cl_2, cm^{-1}): 3002, 2955, 2838, 2255, 1735, 1692, 1517, 1201, 1027, 915, 731, 690. HRMS (ESI+) calcd for $C_{34}H_{34}O_9Na$ $[M+Na]^+$ 609.2101, found 609.2106.

10-methyl-4-phenyl-6,7-dihydro-1*H*-cyclohepta[*f*]isobenzofuran-5(3*H*)-one (**30**)

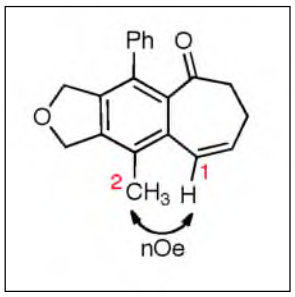
The general procedure **(G3)** was used with 28.20 mg (0.15 mmol) of ether backbone phenyl-methyl diyne, 17.90 mg (0.17 mmol) of tropone, and 3 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 30% ether in pentane (R_f = 0.30) to afford the title compound **30** (35.90 mg, 0.12 mmol) as a light yellow semisolid in 81% yield.



30

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.29-7.39 (m, 3H), 7.23 (m, 2H), 6.64 (d, J = 10.8 Hz, 1H), 6.31 (dt, J = 6.8, 10.8 Hz, 1H), 5.18 (t, J = 1.6 Hz, 2H), 4.98 (t, J = 1.6 Hz, 2H), 2.91 (t, J = 7.2 Hz, 2H), 2.50 (q, J = 7.2 Hz, 2H), 2.22 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 207.2, 140.6, 140.0, 138.9, 138.0, 133.1, 132.5, 131.8, 128.64, 128.60, 128.5, 128.1, 127.7, 74.4, 74.0, 51.0, 23.1, 16.2. IR (CH_2Cl_2, cm^{-1}): 3029,

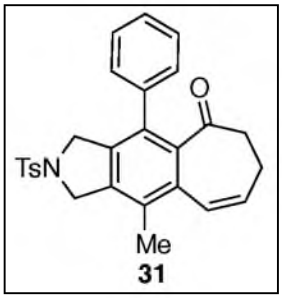
2952, 2852, 1735, 1691, 1597, 1496, 1281, 1035, 754, 665. HRMS (ESI+) calcd for $C_{20}H_{18}O_2Na$ $[M+Na]^+$ 313.1204, found 313.1210.



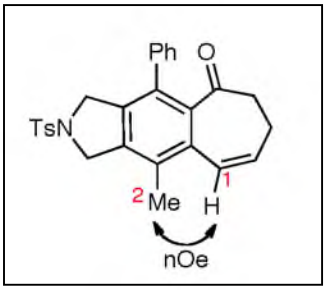
The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.

10-methyl-4-phenyl-2-tosyl-2,3,6,7-tetrahydrocyclohepta [f]isoindol-5(1H)-one (**31**)

The general procedure **(G3)** was used with 45.60 mg (0.14 mmol) of sulfonamide backbone phenyl-methyl diyne, 15.80 mg (0.15 mmol) of tropone, and 3 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 25% ethyl acetate in hexanes (R_f = 0.22) to afford the title compound **31** as an off-white solid (54.30 mg, 0.12 mmol, mp = 210-212 °C) in 91% yield.



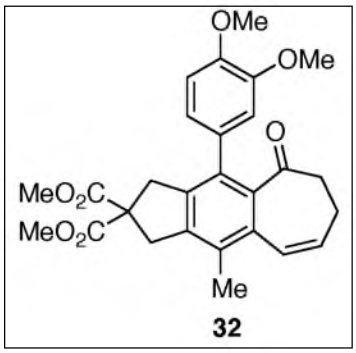
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.74 (d, J = 8.4 Hz, 2H), 7.35 (m, 5H), 7.15 (m, 2H), 6.57 (d, J = 10.8 Hz, 1H), 6.28 (dt, J = 6.8, 10.8 Hz, 1H), 4.66 (s, 2H), 4.43 (s, 2H), 2.83 (t, J = 6.8 Hz, 2H), 2.43 (m, 5H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 206.7, 143.9, 140.9, 138.1, 136.9, 134.9, 133.8, 133.3, 133.0, 132.8, 130.1, 129.4, 128.7, 128.5, 127.9, 127.7, 54.1, 53.9, 50.9, 22.9, 21.7, 15.9. IR (CH_2Cl_2, cm^{-1}): 3031, 2956, 2859, 2255, 1697, 1597, 1347, 1068, 772, 667. HRMS (ESI+) calcd for $C_{27}H_{25}NO_3NaS$ $[M+Na]^+$ 466.1453, found 466.1449.



The regiochemistry was assigned on the basis of nOe of

proton on C-1 with protons on C-2.

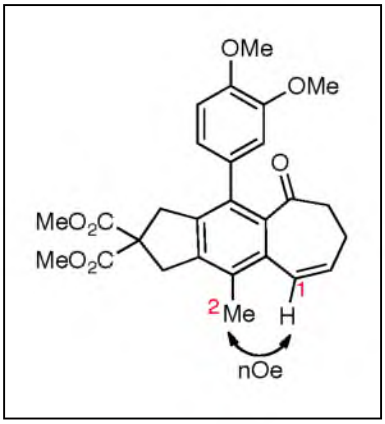
Dimethyl 4-(3,4-dimethoxyphenyl)-10-methyl-5-oxo-3,5,6,7-tetrahydrocyclohepta[f]indene-2,2(1H)-dicarboxylate (**32**)



32

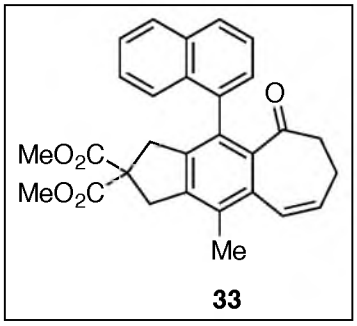
The general procedure **(G3)** was used with 34.90 mg (0.10 mmol) of aryl-alkyl malonate diyne, 11.40 mg (0.11 mmol) of tropone, and 3 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 40% ethyl acetate in hexanes (R_f = 0.28) to afford the title compound **32** as a light yellow oil (40.4 mg, 0.087 mmol) in 89% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.85 (d, J = 8.0 Hz, 1H), 6.79 (d, J = 1.6 Hz, 1H), 6.76 (d, J = 2.0, 8.0 Hz, 1H), 6.61 (d, J = 10.8 Hz, 1H), 6.24 (dt, J = 6.8, 10.8 Hz, 1H), 3.88 (d, J = 4.8 Hz, 6H), 3.74 (s, 6H), 3.64 (s, 2H), 2.44 (s, 2H), 2.86 (t, J = 6.4, 2H), 2.46 (q, J =6.8 Hz, 2H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 207.6, 172.2, 148.8, 148.4, 140.5, 140.4, 138.8, 133.6, 132.5, 131.9, 131.8, 130.4, 129.2, 121.2, 112.7, 111.2, 59.6, 56.1, 56.0, 53.2, 51.2, 40.7, 40.5, 23.0, 16.1. IR (CH_2Cl_2, cm^{-1}): 2955, 1735, 1692, 1606, 1583, 1385, 1252, 1025, 761, 670. HRMS (ESI+) calcd for $C_{27}H_{28}O_7Na$ $[M+Na]^+$ 487.1733, found 487.1729.



The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.

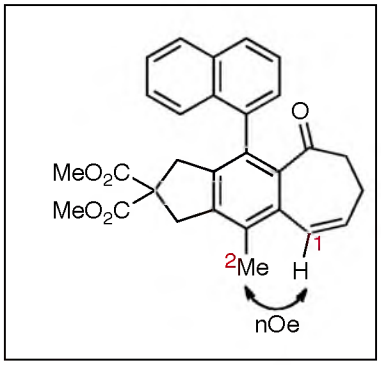
Dimethyl-10-methyl-4-(naphthalen-1-yl)-5-oxo-3,5,6,7-tetrahydro cyclohepta[f]indene-2,2(1H)-dicarboxylate (**33**)



33

The general procedure **(G3)** was used with 38.70 mg (0.11 mmol) of naphthyl-methyl malonate diyne, 13.00 mg (0.12 mmol) of tropone, and 3 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 12 h. The remaining residue was purified by flash column chromatography using 20% ethyl acetate in hexanes (R_f = 0.23) to afford the title compound **33** as a colorless semisolid (45.80 mg, 0.10 mmol) in 91% yield.

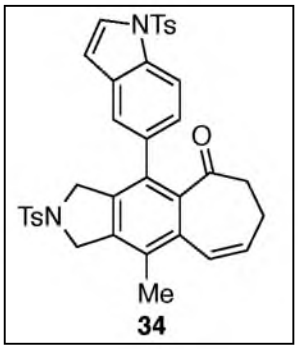
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.87 (m, 1H), 7.83 (d, J = 8.4, 1H), 7.54 dd, J = 0.8, 8.4 Hz, 1H), 7.48 (m, 2H), 7.43(m, 1H), 7.33 (dd, J = 1.2, 6.8 Hz, 1H), 6.67 (d, J = 10.8 Hz, 1H), 6.26 (dt, J = 6.8, 10.8 Hz, 1H), 3.76-3.62 (m, 8H), 3.28-3.05 (dd, J = 17.2, 73.2, 2H), 2.64 (m, 2H), 2.44 (m, 2H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 206.9, 172.1, 141.0, 140.6, 139.6, 136.6, 133.7, 132.5, 132.0, 131.8, 130.9, 129.8, 129.2, 128.5, 128.0, 127.9, 127.0, 126.1, 125.9, 125.8, 125.4, 59.5, 53.13, 53.06, 50.1, 40.5, 40.4, 23.0, 16.2. IR (CH_2Cl_2, cm^{-1}): 3036, 2954, 2361, 2339, 1736, 1692, 1436, 1251, 1164, 1072, 780, 718. HRMS (ESI+) calcd for $C_{29}H_{26}O_5NaS$ $[M+Na]^+$ 477.1678, found 477.1685.



The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.

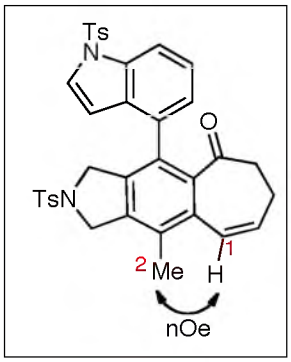
10-methyl-2-tosyl-4-(1-tosyl-1*H*-indol-5-yl)-2,3,6,7-tetrahydrocyclo hepta[*f*]isoindol-5(1*H*)-one (**34**) 4-methyl-2-tosyl-10-(1-tosyl-1H-indol-5-yl)-2,3,6,7-tetrahydrocyclohepta-[f]isoindol-5(1H)-one (**34''**)

The general procedure **(G3)** was used with 68.60 mg (0.13 mmol) of 5-indolyl-methyl malonate diyne, 15.10 mg (0.14 mmol) of tropone, and 10 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 24 h. The remaining residue was purified by flash column chromatography using 35-45% ethyl acetate in hexanes to afford the title compound **34** (52.80 mg, 0.08 mmol) as a yellow semisolid in 64% yield and **34''** (11.5 mg, 0.018 mmol) as a yellow semisolid in 14% yield, respectively.

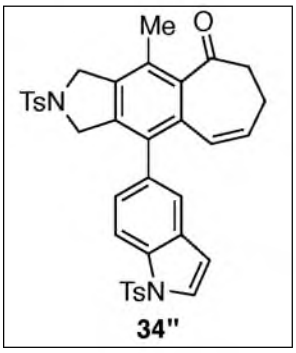


34

[34]: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.95 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 3.6 Hz, 1H), 7.31 (m, 5H), 7.07 (d, *J* = 8.8 Hz, 1H), 6.63 (d, *J* = 6.8, 10.8 Hz, 1H), 6.57 (d, *J* = 10.8 Hz, 1H), 6.27 (dt, *J* = 6.8, 10.8 Hz, 1H), 4.64 (s, 2H), 4.37 (s, 2H), 2.80 (t, *J* = 6.8 Hz, 2H), 2.42 (m, 10 H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 206.7, 145.4, 144.0, 141.2, 136.9, 135.6, 135.3, 134.3, 133.9, 133.1, 132.8, 130.9, 130.3, 130.1, 129.4, 128.5, 127.7, 127.1, 127.0, 125.4, 125.1, 121.4, 113.6, 108.9, 54.2, 53.9, 51.0, 22.9, 21.8, 21.7, 15.9. IR (CH_2Cl_2, cm^{-1}): 3143, 3033, 2955, 2859, 2255, 1692, 1596, 1440, 1371, 1346, 1096, 730, 693. HRMS (ESI+) calcd for $C_{36}H_{32}N_2O_5NaS_2$ $[M+Na]^+$ 659.1650, found 659.1670. The regiochemistry was assigned on the basis of nOe of proton

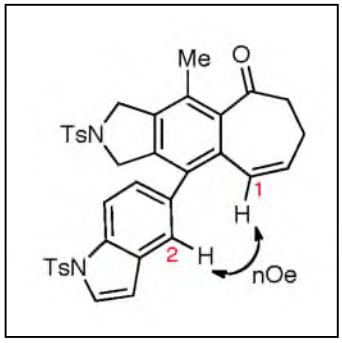


on C-1 with protons on C-2.



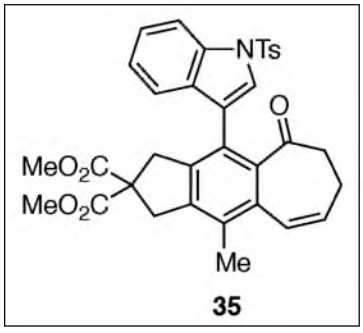
34"

[34"]: ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.59 (d, *J* = 3.6 Hz, 1H), 7.31 (m, 5H), 7.22 (bs, 1H), 6.98 (dd, *J* = 1.6, 8.4 Hz, 1H), 6.62 (d, *J* = 4.0 Hz, 1H), 6.49 (dt, *J* = 4.4, 11.6 Hz, 1H), 6.99 (m, 1H), 4.65 (s, 2H), 4.32 (s, 2H), 3.00 (t, *J* = 6.0 Hz, 2H), 2.40-2.50 (m, 10H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 149.5, 145.4, 143.92, 143.89, 137.6, 136.2, 135.7, 134.5, 134.2, 134.0, 133.3, 132.3, 130.9, 130.3, 130.1, 128.5, 127.7, 127.2, 126.9, 125.2, 121.3, 113.5, 109.0, 54.3, 29.8, 27.9, 21.9, 21.7, 15.9. IR (CH_2Cl_2, cm^{-1}): 3029, 2924, 2856, 2256, 1660, 1596, 1492, 1166, 1096, 703, 667. HRMS (ESI+) calcd for $C_{36}H_{32}N_2O_5NaS_2$ $[M+Na]^+$ 659.1650, found 659.1654.



The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.

Dimethyl 10-methyl-5-oxo-4-(1-tosyl-1H-indol-3-yl)-3,5,6,7-tetrahydrocyclohepta[f]indene-2,2(1H)-dicarboxylate (**35**)

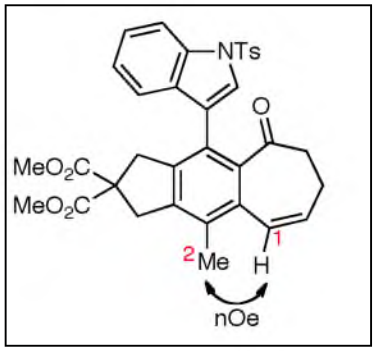


35

The general procedure **(G3)** was used with 45.00 mg (0.09 mmol) of 3-indolyl-methyl malonate diyne, 10.70 mg (0.10 mmol) of tropone, and 3 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 12 h. The remaining residue was purified via flash column chromatography using 55-60% ethyl acetate in hexanes to afford the title compound **35**

(31.0 mg, 0.052 mmol) as a light yellow oil and an inseparable mixture of **35** and its other regioisomer **35''** (10.2 mg, 0.02 mmol) as a yellow oil, in 75% yield.

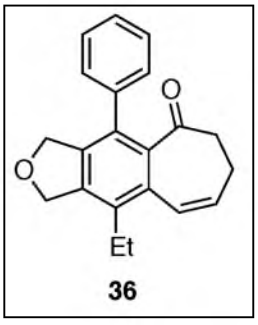
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.49 (s, 1H), 7.19-7.33 (m, 5H), 6.63 (d, J = 10.8 Hz, 1H), 6.25 (dt, J = 6.8, 10.8 Hz, 1H), 3.73 (d, J = 6.0 Hz, 6H), 3.65 (s, 2H), 3.27 (q, J = 17.2 Hz, 2H), 2.68 (m, 2H), 2.41(m, 2H), 2.35 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 206.5, 172.1, 171.9, 145.0, 141.5, 140.9, 140.1, 135.4, 135.1, 132.7, 132.1, 131.5, 130.8, 130.2, 130.0, 129.1, 126.9, 125.2, 125.0, 123.7, 123.4, 120.7, 120.5, 114.1, 59.5, 53.20, 53.16, 50.4, 40.6, 40.5, 23.0, 21.7, 16.2; IR (CH_2Cl_2, cm^{-1}): 3129, 3032, 2954, 2257, 1735, 1691, 1597, 1173, 1095, 730, 690. HRMS (ESI+) calcd for $C_{34}H_{31}NO_7NaS$ $[M+Na]^+$ 620.1719, found 620.1729.



The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.

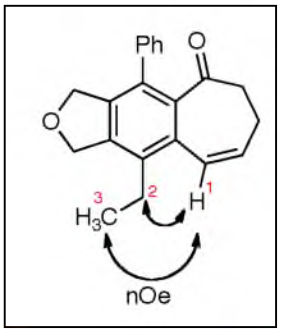
10-ethyl-4-phenyl-6,7-dihydro-1*H*-cyclohepta[*f*]isobenzofuran-5(3*H*)-one (**36**)

The general procedure (**G3**) was used with 32.30 mg (0.16 mmol) of ether backbone phenyl-ethyl diyne, 19.00 mg (0.18 mmol) of tropone, and 3 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 5 h. The remaining residue was purified by flash column chromatography using 25% ether in pentane (R_f = 0.28) to afford the title compound **36** (42.70 mg, 0.14 mmol) as light yellow oil in 86% yield.



36

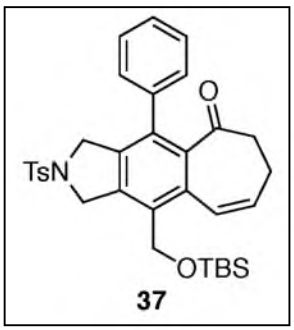
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 (m, 3H), 7.24 (m, 2H), 6.71 (d, *J* = 11.2 Hz, 1H), 6.32 (dt, *J* = 6.8, 11.2 Hz, 1H), 5.21 (t, *J* = 1.6 Hz, 2H), 4.97 (t, *J* = 1.6 Hz, 2H), 2.91 (t, *J* = 6.4 Hz, 2H), 2.60 (q, *J* = 7.6 Hz, 2H), 2.49 (q, *J* = 6.8 Hz, 2H), 1.17 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 207.4, 140.9, 139.4, 138.9, 138.3, 134.4, 132.7, 132.5, 131.9, 128.6, 128.4, 128.3, 127.7, 74.2, 73.5, 51.2, 23.9, 23.0, 14.0. IR (CH_2Cl_2, cm^{-1}): 3030, 2965, 2873, 2249, 1697, 1600, 1496, 1332, 1229, 1092, 770, 732, 581. HRMS (ESI+) calcd for $C_{21}H_{20}O_2Na$ $[M+Na]^+$ 327.1361, found 327.1351.

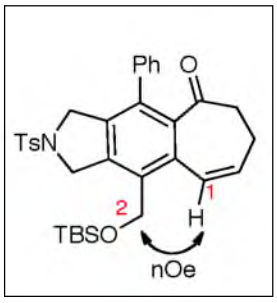


The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2 and C-3.

10-(((*tert*-butyldimethylsilyl)oxy)methyl)-4-phenyl-6,7-dihydro-1*H*-cyclohepta[*f*]isobenzo-furan-5(3*H*)-one (**37**)

The general procedure **(G3)** was used with 38.10 mg (0.08 mmol) of sulfonamide phenyl-silyloxymethyl diyne, 9.50 mg (0.09 mmol) of tropone, and 10 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 12 h. The remaining residue was purified via flash column chromatography starting from 10% to 40% ether in hexanes (R_f = 0.29) to afford the title compound **37** (37.10 mg, 0.07 mmol) as yellow semisolid in 79% yield.





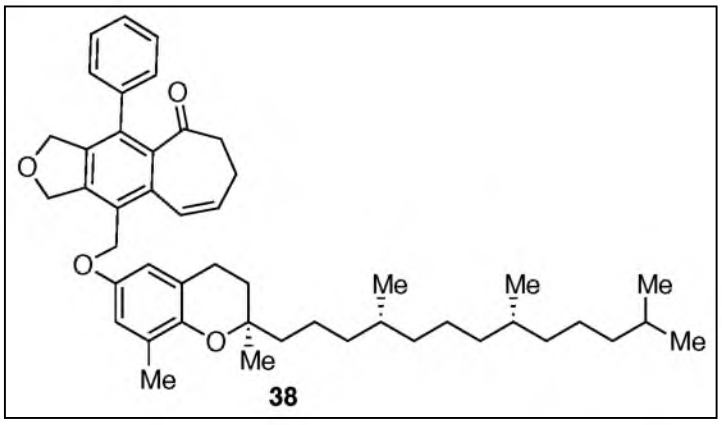
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72 (d, *J* = 8.4 Hz, 2H), 7.35 (m, 5H), 7.14 (dd, *J* = 2.0, 7.6 Hz, 2H), 6 .62 (d, *J* = 11.2

Hz, 1H), 6.30 (dt, J = 7.2, 10.8 Hz, 1H), 4.77 (s, 2H), 4.67 (s, 2H), 4.37 (s, 2H), 2.82 (t, J = 6.4 Hz, 2H), 2.42 (m, 5H), 0.943 (s, 9H), 0.13 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 206.4, 143.9, 141.0, 138.0, 137.0, 136.0, 134.6, 133.7, 133.4, 132.6, 131.7, 130.0, 128.8, 128.4, 128.1, 127.9, 127.8, 60.8, 54.1, 53.4, 51.2, 26.1, 22.6, 21.7, 18.5, 5.2. IR (CH_2Cl_2, cm^{-1}): 3032, 2954, 2930, 2857, 2256, 1696, 1598, 1096, 703, 666. HRMS (ESI+) calcd for $C_{33}H_{39}NO_4NaSSi$ $[M+Na]^+$ 596.2267, found 596.2273.

The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.

10-((((*R*)-2,8-dimethyl-2-((4*R*,8*R*)-4,8,12-trimethyltridecyl)chroman-6-yl)oxy)methyl)-4-phenyl-6,7-dihydro-1*H*-cyclohepta[*f*]isobenzofuran-5(3*H*)-one (**38**)

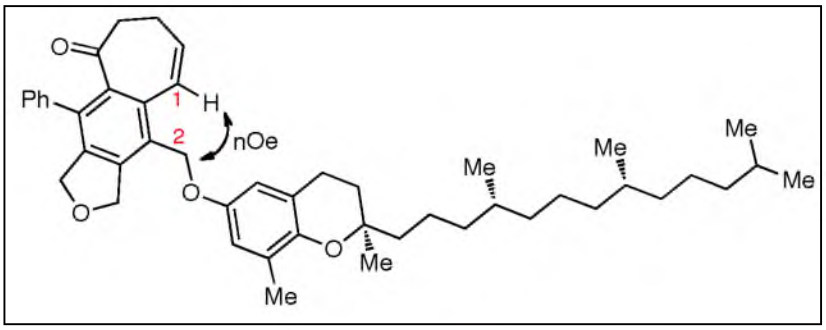
The general procedure **(G3)** was used with 30.60 mg (0.05 mmol) of tocopherol-derived diyne, 6.10 mg (0.06 mmol) of tropone, and 3 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 24 h. The remaining residue was purified by flash column chromatography using 20% ether in hexanes (R_f = 0.18) to afford the title compound **38** (23.40 mg, 0.03 mmol) as yellow oil in 65% yield.



38

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.31-7.41 (m, 3H), 7.23-7.27 (m, 2H), 6.76 (d, J = 11.2 Hz, 1H), 6.64 (d, J = 2.8 Hz, 1H), 6.52 (d, J = 2.8 Hz, 1H), 6.36 (dt, J = 6.8, 11.2

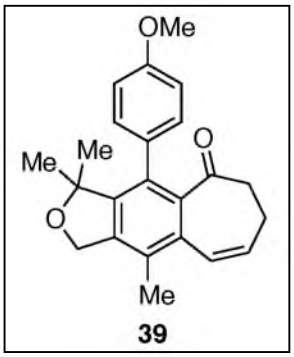
Hz, 1H), 5.31 (s, 2H), 4.97 (s, 2H), 4.94 (s, 2H), 2.92 (t, J = 6.8 Hz, 2H), 2.74 (m, 2H), 2.52 (q, J = 6.8 Hz, 2H), 2.17 (s, 3H), 0.88-1.85 (m, 38H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 206.7, 151.1, 146.9, 140.8, 140.7, 139.2, 138.6, 134.2, 133.6, 133.2, 128.7, 128.4, 128.0, 127.9, 127.6, 127.5, 121.3, 115.6, 112.2, 75.9, 74.0, 73.6, 66.0, 51.2, 40.3, 39.6, 37.7, 37.6, 37.5, 33.0, 32.9, 31.5, 28.2, 25.0, 24.7, 24.4, 22.9, 22.8, 21.2, 20.0, 19.9, 16.5. IR (CH_2Cl_2, cm^{-1}): 2927, 2863, 2361, 1695, 1605, 1478, 1121, 1182, 1066, 702. HRMS (ESI+) calcd for $C_{47}H_{62}O_4Na$ $[M+Na]^+$ 713.4546, found 713.4539.



The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.

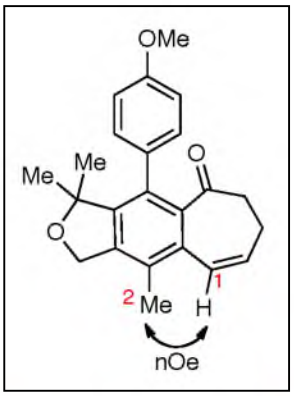
4-(4-methoxyphenyl)-3,3,10-trimethyl-6,7-dihydro-1H-cyclohepta [f]isobenzofuran-5(3H)-one (**39**)

The general procedure **(G3)** was used with 45.60 mg (0.19 mmol) of ether backbone diyne, 22.00 mg (0.21 mmol) of tropone, and 10 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 12 h. The remaining residue was purified via flash column chromatography starting from 25-30% ether in hexanes (R_f = 0.21) to afford the title compound **39** (45.9 mg, 0.13 mmol, mp = 148-150 °C) as a light yellow solid in 70% yield.



39

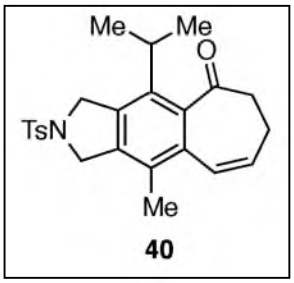
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.13 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 2H), 6.64 (d, J = 10.8 Hz, 1H), 6.25 (dt, J = 6.8, 10.8 Hz, 1H), 5.04 (s, 2H), 3.83 (s, 3H), 2.73 (t, J = 6.4 Hz, 2H), 2.41 (q, J = 6.8 Hz. 2H), 2.19 (s, 3H), 1.24 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 207.5, 159.1, 144.1, 142.2, 139.7, 132.4, 132.3, 131.6, 131.1, 129.2, 128.9, 128.0, 113.0, 87.9, 69.7, 53.3, 51.1, 28.4, 23.1, 15.7. IR (CH_2Cl_2, cm^{-1}): 3031, 2968, 2933, 2361, 1695, 1611, 1459, 1141, 872, 612, 541. HRMS (ESI+) calcd for $C_{23}H_{24}O_3Na$ $[M+Na]^+$ 371.1623, found 371.1634.



The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.

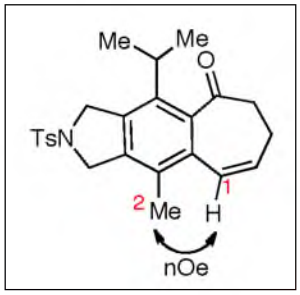
10-isopropyl-4-phenyl-2-tosyl-2,3,6,7-tetrahydrocyclohepta[f] isoindol-5(1H)-one (**40**)

The general procedure **(G3)** was used with 48.00 mg (0.16 mmol) of sulfonamide isopropyl-methyl diyne, 20.10 mg (0.19 mmol) of tropone, and 3 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 12 h. The remaining residue was purified by flash column chromatography starting from 10% to 40% ether in hexanes (R_f = 0.23) to afford **40** (49.9 mg, 0.12 mmol) as a yellow semisolid in 77% yield.



40

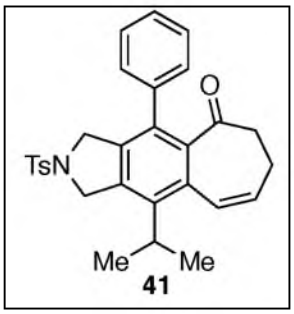
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.79 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 6 .50 (d, J = 10.8 Hz, 1H), 6.23 (dt, J = 6.8, 10.8 Hz, 1H), 4.74 (s, 2H), 4.53 (s, 2H), 2.98 (t, J = 6.8 Hz, 2H), 2.86 (septet, J = 7.2 Hz, 1H), 2.42 (s, 3H), 2.34 (q, J = 6.8 Hz, 2H),



2.08 (s, 3H), 1.21 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 209.2, 144.0, 140.3, 137.6, 137.0, 133.8, 133.6, 133.1, 132.4, 130.1, 128.8, 127.9, 127.7, 54.0, 53.0, 51.3, 31.8, 22.9, 21.9, 21.7, 15.6. IR (CH_2Cl_2, cm^{-1}): 2962, 1692, 1597, 1449, 1347, 1098, 730, 667. HRMS (ESI+) calcd for $C_{24}H_{27}NO_3NaS$ $[M+Na]^+$ 432.1609, found 432.1617.

The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2.

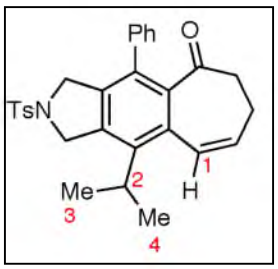
10-isopropyl-4-phenyl-2-tosyl-2,3,6,7-tetrahydrocyclohepta[f] isoindol-5(1H)-one (**41**)



The general procedure **(G3)** was used with 30.60 mg (0.08 mmol) of sulfonamide phenyl-isopropyl diyne, 9.80 mg (0.09 mmol) of tropone, and 5 mol % of catalyst in THF. The reaction mixture was heated at 60 °C for 10 h. The remaining residue was purified by silica gel flash column chromatography starting from 10% to 40% ether in hexanes (R_f = 0.17) to afford the title compound **41** (30.0 mg, 0.06 mmol) as a yellow semisolid in 76%.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72 (d, J = 8.4 Hz, 2H), 7.35 (m, 5H), 7.13 (dd, J = 1.2, 7.6 Hz, 2H), 6 .70 (d, J = 10.8 Hz, 1H), 6.26 (dt, J = 7.2, 10.8 Hz, 1H), 4.77 (s, 2H), 4.32 (s, 2H), 3.22 (septet, J = 6.8 Hz, 1H), 2.78 (t, J = 6.8 Hz, 2H), 2.43 (s, 3H), 2.38 (q, J = 6.8 Hz, 2H), 1.26 (d, J = 7.6 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 207.0, 144.0, 141.5, 139.5, 138.0, 136.3, 135.3, 133.8, 132.7, 132.6, 132.4, 130.1, 129.4, 128.7, 128.5, 128.0, 127.6, 54.0, 53.1, 51.8, 30.4, 22.2, 21.7, 21.2. IR (CH_2Cl_2, cm^{-1}):

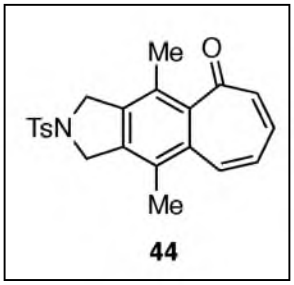
3032, 2964, 2871, 2255, 1695, 1598, 1347, 1097, 704, 668, 548. HRMS (ESI+) calcd for $C_{29}H_{29}NO_3NaS$ $[M+Na]^+$ 494.1766, found 494.1764.



The regiochemistry was assigned on the basis of nOe of proton on C-1 with protons on C-2, C-3 and C-4.

4,10-dimethyl-2-tosyl-2,3-dihydrocyclohepta[f]isoindol-5(1H)-one (**44**)

To a solution of 156.60 mg (0.41 mmol) of **23** in 4 ml of EtOH was added 16.00 mg of 5 wt% of Pd/C. The reaction was stirred under atmospheric pressure of H_2 (balloon) at room temperature for overnight. The reaction mixture was filtered through a short pad of celite and the solvents were evaporated *in vacuo*. The product obtained (**42**) was dissolved in 1.3 ml of dry CCl_4 and stirred under an atmosphere of nitrogen. Bromine (98.50 mg, 0.62 mmol) was dissolved in 0.4 ml of CCl_4 and dropwise added to the reaction mixture at room temperature. Upon completion of the addition, the mixture was stirred at room temperature for 30 min and then brought to reflux for 1 h. The solvent was removed *in vacuo* and the residue was dissolved in 3.7 ml of dry DMF followed by the addition of LiCl (50.00 mg, 1.17 mmol) under an atmosphere of nitrogen. The reaction mixture was refluxed for 2 h under and worked up by the addition of water and extraction with CH_2Cl_2. The organic layers were washed with brine and then dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* and the crude product was purified by silica gel flash chromatography using 25-30% ether in hexanes (R_f = 0.22) to obtain the title compound **44** (62.2 mg, 0.164 mmol, decomposition > 210 °C) in 40% yield.



44

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.81 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 12.0 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.82 (dd, *J* = 6.8, 11.6 Hz, 1H), 6.67 (m, 2H), 4.71 (d, *J* = 7.6 Hz, 4H), 2.42 (s, 3H), 2.38 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 194.1, 144.1, 140.4, 138.3, 137.8, 134.0, 133.0, 133.2, 131.7, 131.4, 130.2, 129.4, 128.1, 127.8, 126.4, 54.5, 54.4, 21.7, 17.5, 17.1. IR (CH_2Cl_2, cm^{-1}): 2925, 2854, 1731, 1598, 1557, 1268, 1100, 867, 781, 582. HRMS (ESI+) calcd for $C_{22}H_{21}NO_3NaS$ $[M+Na]^+$ 402.1140, found 402.1157.

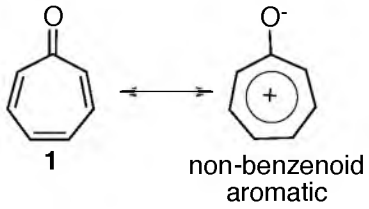
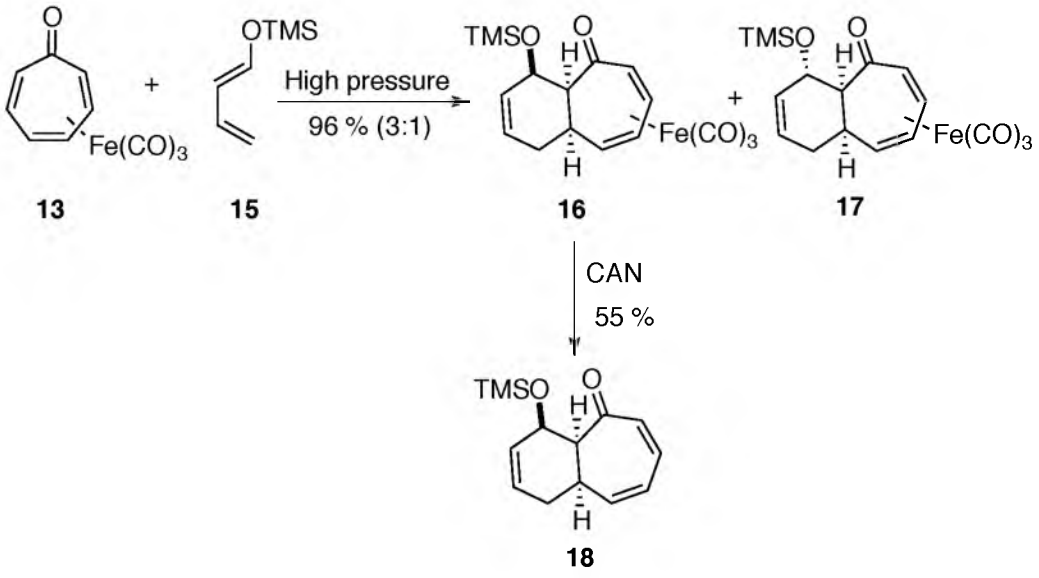


Figure 5.1 Resonance forms of tropone **1**



Scheme 5.1 Existing strategy to utilize single C-C π bond of tropone

Table 5.1 Ni-catalyzed cycloaddition of diyne with tropone[a]

Entry	L	Ni:L_n	% Conv. of **19**[b]	% Yield of **20**[b]
1	PPh_3	1:2	>99	14
2	PCy_3	1:2	>99	29
3	$P(Oi\text{-}Pr)_3$	1:2	>99	14
4	PPh_2Me	1:2	>99	9
5	$P(o\text{-tolyl})_3$	1:2	>99	3
6	DPPF	1:1	>99	4
7	BINAP	1:1	85	6
8	DPPB	1:1	>99	6
9	Xantphos	1:1	>99	-
10	*t*-Bu-Xantphos	1:1	>99	-
11	IMes	1:2	96	79
12	I^tBu	1:2	98	71
13	IPr	1:2	>99	>99 (**92**)[c]
14	SIPr	1:2	>99	>99 (**95**)[c]

[a]Reaction conditions: 10 mol % $Ni(cod)_2$, 20 mol % L_n, diyne (1 equiv, 0.1M), tropone (1.1 equiv), toluene, 60 °C, 5 h. [b]Determined by GC using naphathalene as an internal standard. [c]Isolated yield.

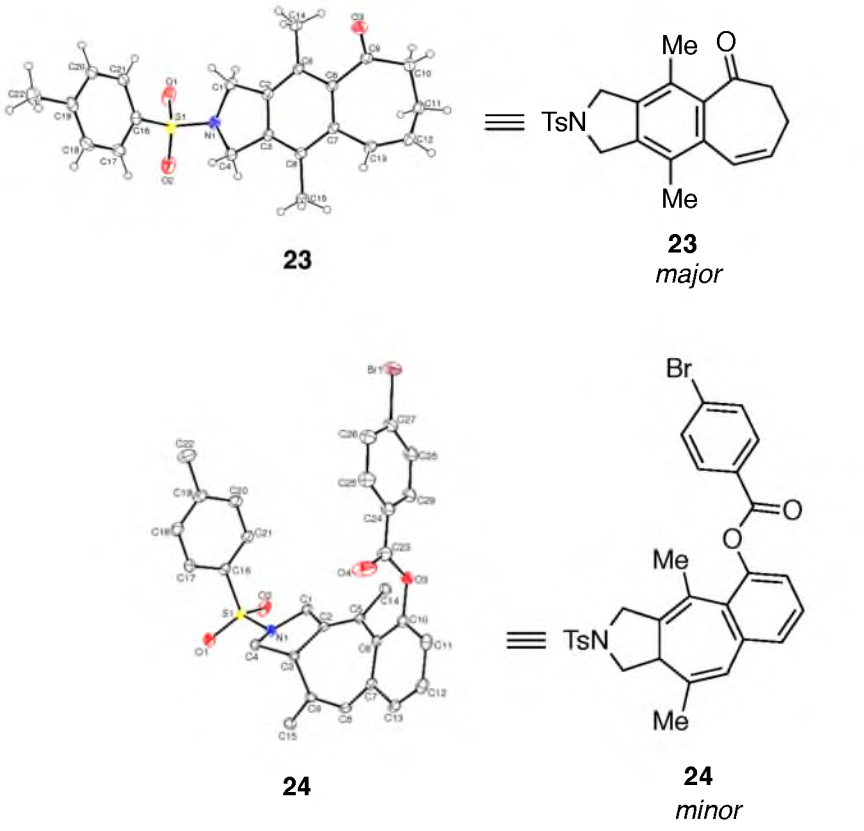
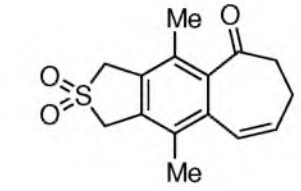
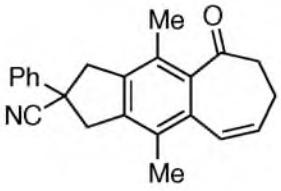


Figure 5.1 Ortep diagram of **23** (major) and **24** (minor)

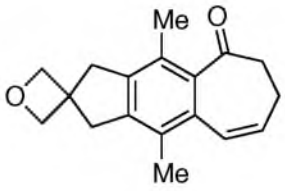
Table 5.2 Ni-catalyzed cycloaddition of diynes and tropone[a,b]



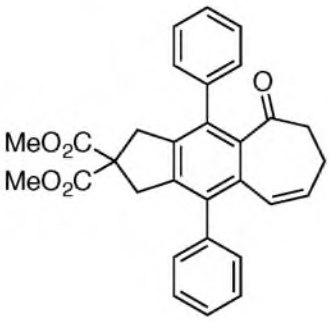
25, 67%
[1:0.06][c]



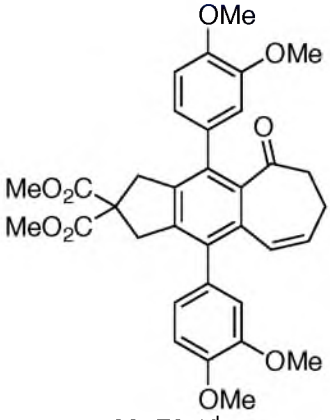
26, 97%
[1:0.08][c]



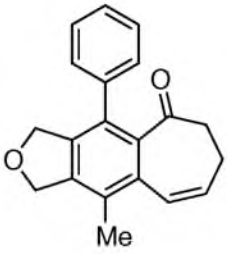
27, 87%
[1:0.25][c]



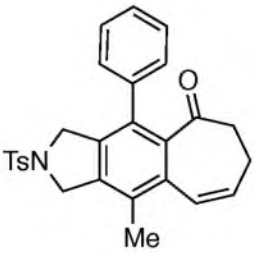
28, 64%



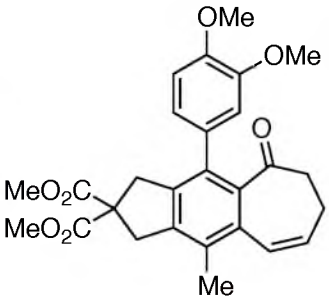
29, 72%[d]



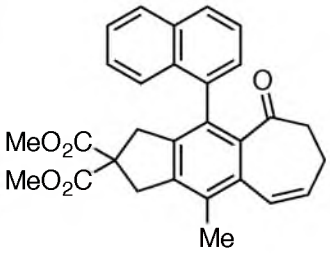
30, 81%
[>95%][c]



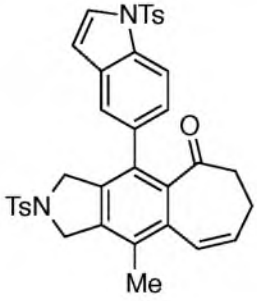
31, 91%
[>95%][c]



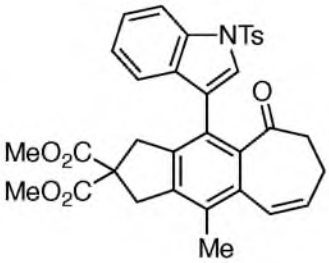
32, 89%
[>95%][c]



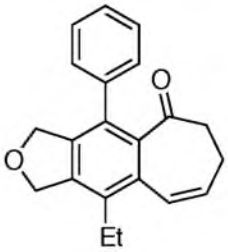
33, 91%
[>95%][c]



34, 78%
[82:18][c]

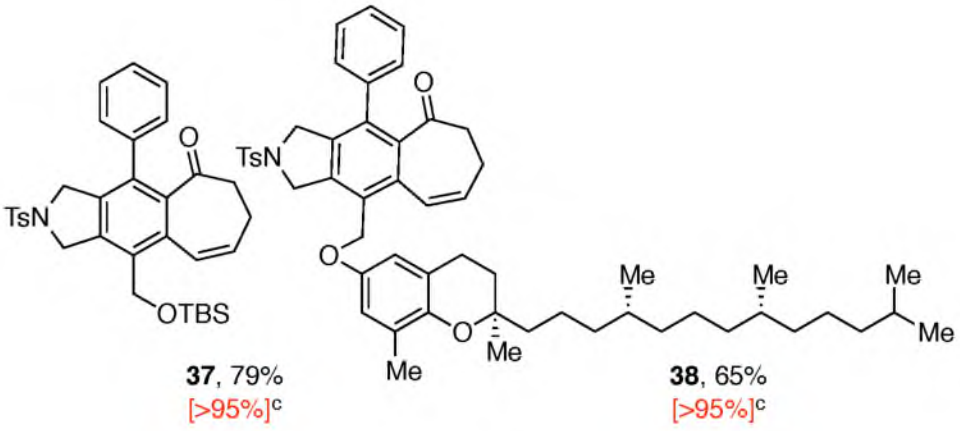


35, 75%
[93:7][c]



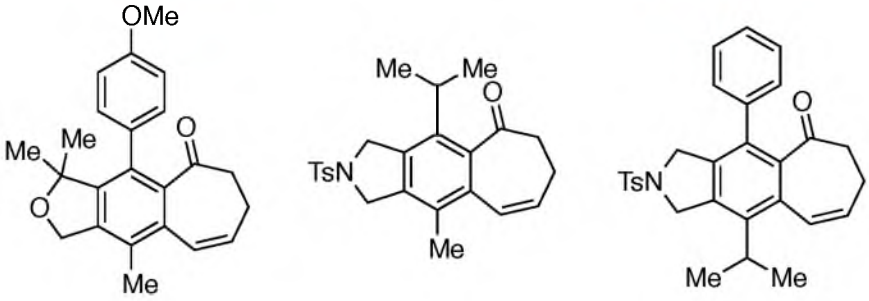
36, 86%
[>95%][c]

Table 5.2 Continued



37, 79%
[>95%][c]

38, 65%
[>95%][c]

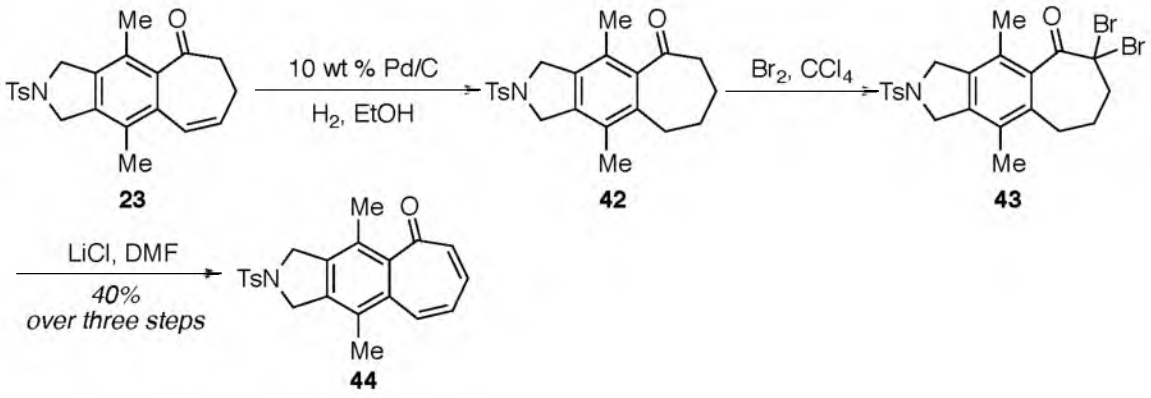


39, 70%
[>95%][c]

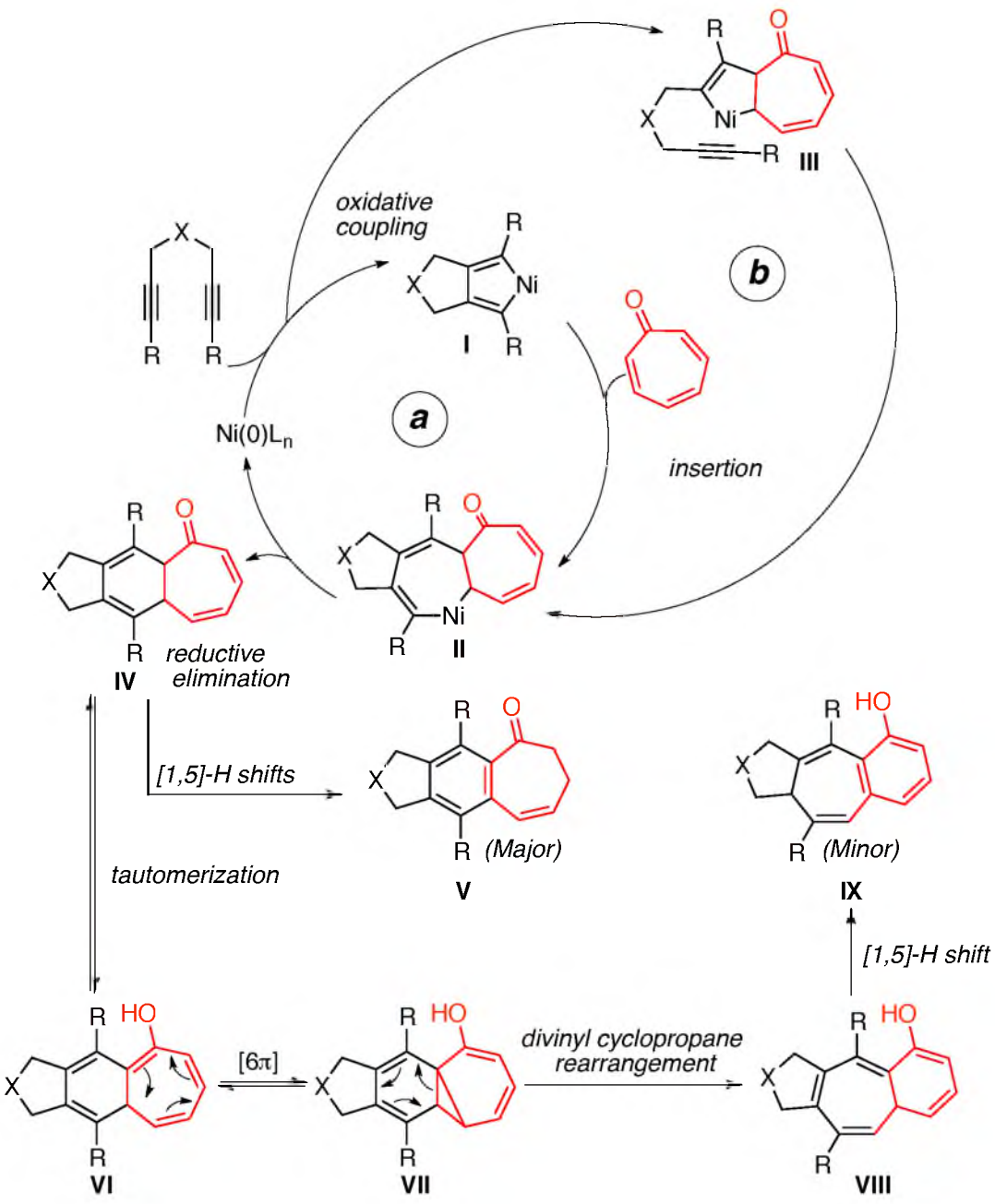
40, 77%
[93:7][c]

41, 76%
[>95%][c]

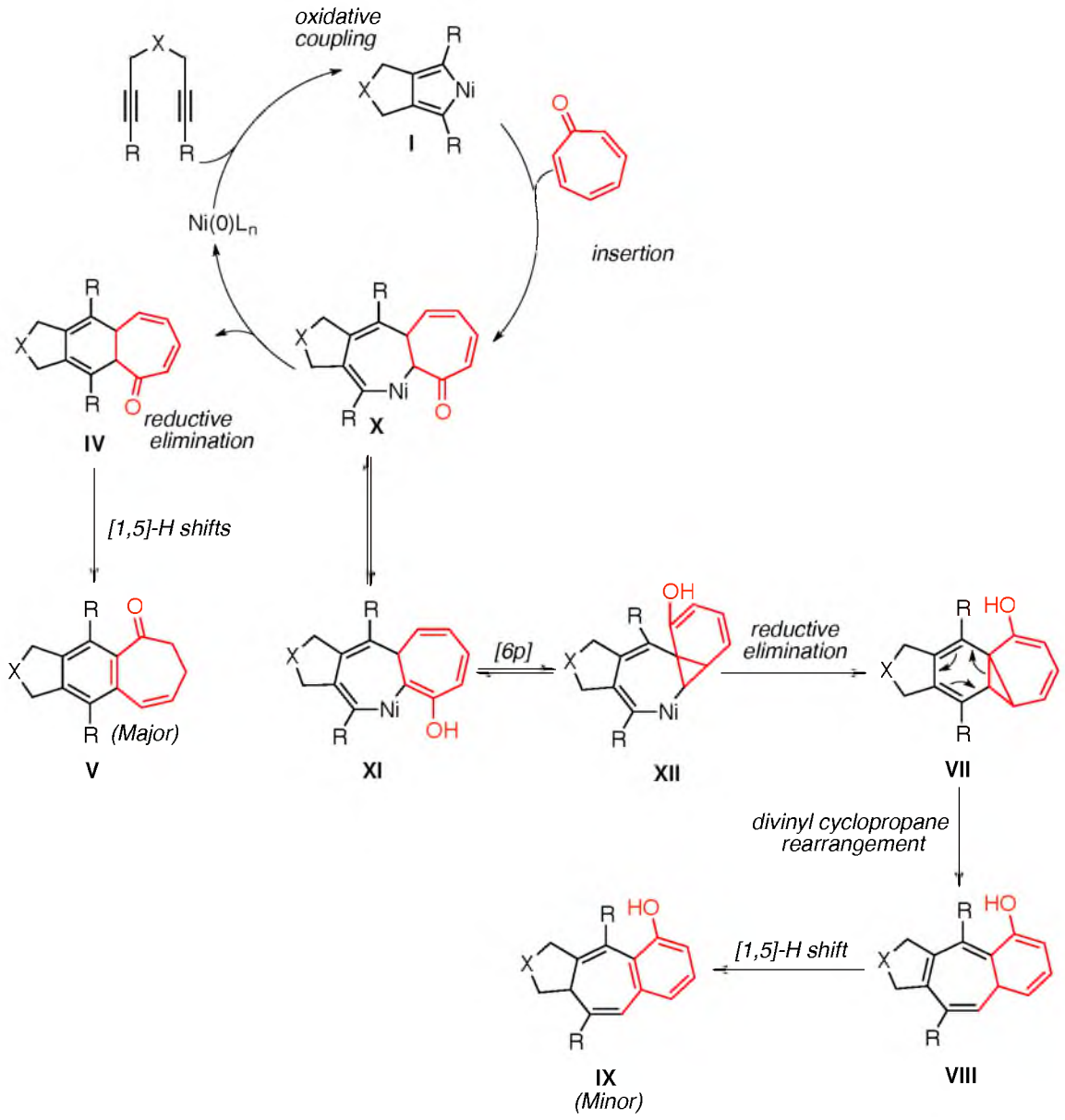
[a]Reaction conditions: diyne (1 equiv, 0.1 M), tropone (1.2 equiv), 3 mol % $Ni(COD)_2$, 6 mol % SIPr, THF, 60 °C, 5 h. [b]Isolated yields (in black), ratio of major and minor cycloadduct (in blue), regioselectivity (in red). [c]The ratios were determined by ^{1}HNMR of crude reaction mixture. [d]The reaction was performed with 10 mol % catalyst loading at room temperature.



Scheme 5.2 Conversion of cycloadduct **23** to troponoid **44**



Scheme 5.3 Proposed mechanism of Ni-catalyzed cycloaddition of diynes with tropone



Scheme 5.4 Proposed mechanism of Ni-catalyzed cycloaddition of diynes with tropone supported by computational calculations

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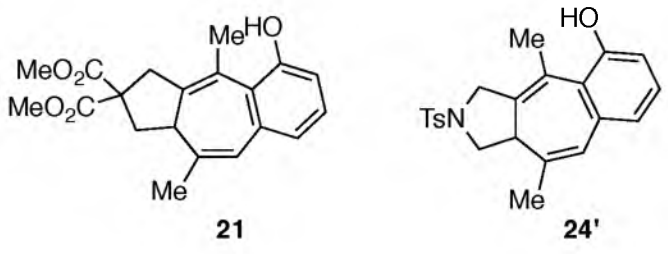
(11) This analysis reveals the identity of **21** and **24** as:



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